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ANTIBIOTIC RESISTANCE AND THE USE OF ANTIBIOTICS IN ANIMAL AGRICULTURE

HEARING

BEFORE THE

SUBCOMMITTEE ON HEALTH

OF THE

COMMITTEE ON ENERGY AND COMMERCE

HOUSE OF REPRESENTATIVES

ONE HUNDRED ELEVENTH CONGRESS

SECOND SESSION

JULY 14, 2010

Serial No. 111–144



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ANTIBIOTIC RESISTANCE AND THE USE OF ANTIBIOTICS IN ANIMAL AGRICULTURE

WEDNESDAY, JULY 14, 2010

HOUSE OF REPRESENTATIVES,
SUBCOMMITTEE ON HEALTH,
COMMITTEE ON ENERGY AND COMMERCE,
Washington, DC.

The subcommittee met, pursuant to call, at 2:12 p.m., in Room 2123 of the Rayburn House Office Building, Hon. Frank Pallone, Jr. [Chairman of the Subcommittee] presiding.

Members present: Representatives Pallone, Dingell, Schakowsky, Baldwin, Barrow, Christensen, Murphy of Connecticut, Space, Braley, Waxman (ex officio), Shimkus, Buyer, Pitts, Sullivan, Murphy of Pennsylvania, Blackburn and Gingrey.

Staff present: Ruth Katz, Chief Public Health Counsel; Sarah Despres, Counsel; Rachel Sher, Counsel; Stephen Cha, Professional Staff Member; Emily Gibbons, Professional Staff Member; Virgil Miler, Professional Staff Member; Alvin Banks, Special Assistant; Allison Corr, Special Assistant; Eric Flamm, FDA Detailee; Karen Lightfoot, Communications Director, Senior Policy Advisor; Elizabeth Letter, Special Assistant; Lindsay Vidal, Special Assistant; Mitchell Smiley, Special Assistant; Clay Alspach, Minority Counsel, Health; and Ryan Long, Minority Chief Counsel, Health.

OPENING STATEMENT OF HON. FRANK PALLONE, JR., A REPRESENTATIVE IN CONGRESS FROM THE STATE OF NEW JERSEY

Mr. PALLONE. The meeting of the Health Subcommittee is called to order, and the subcommittee is convening today for its third hearing to discuss antibiotic resistance and its threat to public health. Today we will examine the use of antibiotics in food-producing animals and the impact of this use on human health.

Antibiotics, as you all know, are among the most significant medical innovations of the 20th century. The CDC lists control over infectious disease as one of its top 10 great public health achievements of the last century, and antimicrobials are crucial to that accomplishment. And yet we must collectively be alarmed that we are undermining the power of antibiotics by failing to use them judiciously. In past hearings, we have heard testimony about physicians that are prescribed antibiotics just in case their patients have bacterial infections, and we all know patients that have stopped taking their antibiotics once they felt better, even if they didn't finish the treatment. It is clear that the consequences of such actions are severe. Manmade antimicrobial resistance weakens our options

to treat pneumonia, food-related diseases including E. coli and Salmonella, and hospital-acquired infections, commonly known as MRSA.

Our examination of antibiotic resistance would not be complete without a discussion of the use of antimicrobials in animals. It is very timely that we are having this hearing today. Last month the FDA issued draft guidance detailing its position that using medically important antimicrobial drugs for food production purposes threatens the protection and promotion of the public health. FDA will state today that antibiotics should only be given to animals under supervision of a veterinarian and should only be used to assure animal health and not to promote growth. We will have the opportunity today to hear from the major experts and stakeholders in the field about reactions to FDA's draft guidance and the overall debate on how animal use of antibiotics impacts human health.

As we consider future action to limit antibiotic resistance, it would be helpful to hear about the Danish experience. Starting in 1995, the Danish government implemented aggressive steps to limit the use of antibiotics in food-producing animals and collected extensive data that they and the World Health Organization used to evaluate the effects of these actions. Clearly, any future action to limit antibiotic resistance must be carefully considered and guided by science.

We have two great panels today of government and private witnesses with 10 people total testifying who will contribute to this discussion, and I know that many of the witnesses rearranged their schedules today to be here including Dr. Josh Sharfstein at the FDA. We greatly appreciate your ability. However, I am going to have to say one thing you are not going to like, and that is that unfortunately as too many times has been the case here, we did not get the testimony within 48 hours before the hearing. I know that the hearing was changed, I guess, from tomorrow to today but we notified everybody 3 weeks ago of that, and the FDA testimony arrived at about 6 p.m. Tuesday, which was last night, and the CDC testimony also arrived late in the day on Tuesday, which obviously doesn't make the 48 hours, so please in the future, it is really important that we get the testimony 48 hours before the hearing. Otherwise we really can't adequately prepare for the hearing, so I just want to mention that, and I don't want to be difficult but it really is important.

[The prepared statement of Mr. Pallone follows:]

Chairman Frank Pallone
Antibiotic Resistance and the Use of Antibiotics in Animal Agriculture
June 14, 2010

Good afternoon. The Subcommittee is convening today for its third hearing to discuss antibiotic resistance and its threat to public health. Today we will examine the use of antibiotics in food-producing animals and the impact of this use on human health.

Antibiotics are among the most significant medical innovations of the 20th century. The CDC lists "control over infectious disease" as one of its top 10 "great public health achievements" of the last century and mentions antimicrobials as crucial to that accomplishment.

And yet, we must collectively be alarmed that we are undermining the power of antibiotics by failing to use them judiciously. In past hearings we have heard testimony about

physicians that have prescribed antibiotics "just in case" their patients have bacterial infections. And we all know patients that have stopped taking their antibiotics once they felt better-even if they didn't finish the treatment. It is clear that the consequences of such actions are severe—man made antimicrobial resistance weakens our options to treat pneumonia, food-related diseases including e-coli and salmonella, and hospital-acquired infections commonly known as MRSA [mer-sa].

Our examination of antibiotic resistance would not be complete without a discussion of the use of antimicrobials in animals. It is very timely that we are having this hearing today; last month, the Food and Drug Administration issued draft guidance detailing its position that using medically important antimicrobial drugs for food production purposes threatens the protection and promotion of the public health. FDA will state today that antibiotics should only be given to animals under the

supervision of a veterinarian and should only be used to assure animal health—and not to promote growth.

We will have the opportunity today to hear from the major experts and stakeholders in the field today about reactions to FDA's draft guidance, and the overall debate on how animal use of antibiotics impacts human health.

As we consider future action to limit antibiotic resistance, it will be helpful to hear about the "Danish Experience." Starting in 1995, the Danish government implemented aggressive steps to limit the use of antibiotics in food-producing animals, and collected extensive data that they and the World Health Organization used to evaluate the effect of these actions.

Clearly, any future action to limit antibiotic resistance must be carefully considered and guided by Science. We have two great

panels today of government and private witnesses—with 10 people total testifying.

I know that many of the witnesses re-arranged their schedules to be here today, including Dr. Josh Sharfstein of the FDA. We appreciate your flexibility and I am certain that we will gain some valuable information today.

And now, a statement from our Ranking Member, Mr. Shimkus.

#

Mr. PALLONE. With that, I will yield to our ranking member, the gentleman from Illinois, Mr. Shimkus.

OPENING STATEMENT OF HON. JOHN SHIMKUS, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF ILLINOIS

Mr. SHIMKUS. Thank you, Mr. Chairman, and thank you for obviously the admonition about getting testimony in, and I appreciate that. I know it is not easy.

Thank you all for coming. The debate centers around whether antibiotic use in animals presents a safety risk for humans. Rather than focus on theory, we must really rely on the science behind the issue. So far there is nothing that links use in animals to a build-up of human resistance, and so I will be focusing on, I know it sounds crazy, but real science, real peer-reviewed science and testing, which in previous testimony, and I have the record from the previous hearings that we have done none in this country. There has been no testing in this country on this connection. So the challenge will be to not move in public policy until we have verifiable peer-reviewed science to address this issue.

We do know through the hearings that people are overusing and misusing antibiotics and that leads to faster development of resistance of drugs in the body, and when it comes to people getting sick from foodborne antibiotic-resistant strains, evidence shows it is again from humans through handling food, not animals. Even then because of our rigorous oversight, foodborne illnesses in the United States have continued to decline over the past decade. Nevertheless, as science develops and we learn more, we can always work to improve risk-based approach to making people and the foot they eat safer. We should explore ways to strengthen our hazardous analysis and critical control points, plans across the spectrum from farm to fork.

At the same time, FDA should continue its strict approval path of antibiotics for animal use. The FDA process is resulting in increasing amounts of approved antibiotics that are not used in human medicine at all. As a result, those classes of antibiotics have no potential impact on human resistance while yielding benefits on the farm. Still, there are some who would ban use of antibiotics in animals similar to what occurred in Denmark in the late 1990s, and I know the chairman mentioned that, and I will be talking about that research too. Since the ban, Danish animals' death and diseases have increased. To control these increases, therapeutic use of antibiotics to treat sick animals more than doubled to a level greater than all antibiotic use combined prior to the year of the ban. So they banned it and we use more. Animals are not healthier; they are sicker. So that is why we do appreciate this hearing, and this question, we did make humans safer? No. Only did humans not become any less resistant, they became more resistant to antibiotics in Denmark. Resistance increased in Salmonella, penicillin, tetracycline. At the same time those resistances in the United States have decreased to about half the level of Denmark. Before we go down a path that will have a devastating economic impact on our agriculture industry, we must ensure science drives this debate.

So again, I want to thank you, Mr. Chairman, for holding this hearing.

The last thing I do want to mention is that we have 10 witnesses today. This is our third or fourth hearing on antibiotics. We have not had a single hearing on the new health care law passed. We have asked for the CMS actuary. We have asked for Secretary Sebelius. Now we have a recess appointment, Dr. Berwick, who we like to see, who said some interesting things about rationing care and that we would do it with our eyes open, but I guess what is as telling as anything else why we need to have a hearing is, it seems that in the $160 million that we provided to Pennsylvania for the high-risk pool, abortion and abortion services are being expanded at taxpayers' expense. I thought this was a promise made to the pro-life Democrats in voting for the bill through the Executive Order. Obviously that was not the case and that is why we should have a hearing, and I yield back my time.

Mr. PALLONE. Thank you, Mr. Shimkus.

The chairman of our full committee, the gentleman from California, Mr. Waxman.

OPENING STATEMENT OF HON. HENRY A. WAXMAN, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF CALIFORNIA

Mr. WAXMAN. Thank you very much, Mr. Chairman. I am pleased you are holding this third of a series of hearings on antibiotic resistance. This is a serious public health problem.

Our first hearing provided the context for understanding the nature of the problem, the scope, the statistics and the science that make up this emerging public health crisis. The focus of today's hearing, the use of antibiotics in animals, is an issue that has been raised by numerous members of this subcommittee as well many of our previous witnesses, representing both the public and private sectors, and I think we would all agree that the topic is complicated and controversial.

I believe we would also all agree on this point: By definition, antibiotic resistance is bred by the very use of antibiotics, be it by humans or by animals. To remain effective, then, antibiotics need to be used judiciously.

As we learned at our last hearing, antibiotics are being overprescribed in humans. That is a very real and difficult problem and one that requires our full and immediate attention.

But the issue with animals is something else. For animals, we use antibiotics for purposes other than treating illnesses in the animal. As we will hear today, animals raised for food production are routinely provided antibiotics to prevent infections. In stark contrast to animals, we would be shocked if a pediatrician ever ordered antibiotics for an entire nursery school class to keep the children from being infected with strep throat. But in this country, that is standard practice for a barnyard full of pigs or cows or chickens. In addition, animals regularly are fed these drugs not to treat any illness at all but simply to promote growth. In both situations, this is an overprescribing of a very different sort.

There appears to be universal agreement on yet another point: The key to reducing antibiotic resistance is to reduce the use of

antibiotics. The Food and Drug Administration recently announced one approach for achieving this goal with respect to animals. In June, the agency issued draft guidance which recommends that antibiotics not be given to animals to promote growth and that when these drugs are used, they should be administered only under the supervision of a veterinarian. This sounds to me like a very good first step.

But we must do more to tackle this piece of the antibiotic resistance puzzle and we must do so as part of a comprehensive strategy designed to safeguard the vitally important public health tool that is our antibiotics. I would like to put into the record a letter from Dr. Frieden, the director of the Centers for Disease Control to Chairman Pallone, and according to Dr. Frieden, "The Centers for Disease Control and Prevention finds there is a compelling body of evidence to demonstrate this link between antibiotic use in animals and the resistance from the antibiotics."

[The information appears at the conclusion of the hearing.]

Mr. PALLONE. Without objection, so ordered.

Mr. WAXMAN. It is critical we encourage the development of new drugs. It's also essential to preserve the antibiotics we already have. That means we must move expeditiously to slow the advancement of antibiotic resistance in both humans and animals. In each instance, our strategy must be based on science. I agree with that statement. But science, not just the science that may fit our constituency but real science and the scientific evidence is now strong enough to create a consensus among major public health groups and experts around the world that the time has come to reduce the use of antibiotics in animals. Organizations as diverse as the American Medical Association, the Institute of Medicine, the World Health Organization, and as we will hear from both CDC and the FDA, they all agree: We must take action now.

This brings us to today's hearing. It is an important hearing. Mr. Chairman, I want to thank Dr. Sharfstein. He has been very accommodating to be here today. He accommodated us by rearranging his schedule. I happen to know that by watching television he has been very busy. I didn't see him out in Los Angeles at any of the beaches, so I think he has been working pretty hard and I have noticed he has been involved in Avandia. We would like those statements in earlier, but I think they ought to cut you a little slack. At least I am going to make that comment. And the same is true for others but we do need these statements as early as possible.

I thank all the witnesses who are here. I particularly thank you, Mr. Chairman, for this hearing. I think this is going to be an interesting one. Let us follow the science. Thank you. Yield back.

[The prepared statement of Mr. Waxman follows:]

Statement of Chairman Henry A. Waxman
Committee on Energy and Commerce
Subcommittee on Health
Hearing on "Antibiotic Resistance and the Use of Antibiotics in Animal Agriculture"
July 14, 2010

Thank you, Mr. Chairman, for holding today's hearing, the third in the Subcommittee's series to examine the growing and serious problem of antibiotic resistance.

Our first hearings provided the context for understanding the nature of the problem – the scope, the statistics, and the science that make up this emerging public health crisis.

The focus of today's hearing -- the use of antibiotics in animals -- is an issue that has been raised by numerous Members of the Subcommittee as well many of our previous witnesses, representing both the public and private sectors. I think we would all agree that the topic is complicated and controversial.

I believe we would also all agree on this point: By definition, antibiotic resistance is bred by the very use of antibiotics, be it by humans or by animals. To remain effective, then, antibiotics must be used judiciously.

As we learned at our last hearing, antibiotics are being overprescribed for use in humans. That is a very real and difficult problem and one that requires our full and immediate attention.

But the issue with animals is something else. For animals, we use antibiotics for purposes other than treating disease.

As we will hear today, animals raised for food production are routinely provided antibiotics to prevent infections. In stark contrast to animals, we would be shocked if a pediatrician ever ordered antibiotics for an entire nursery school class to keep the children from being infected with strep throat. But in this country, that is standard practice for a barnyard full of pigs, or cows, or chickens. In addition, animals regularly are fed these drugs -- not to treat any illness at all -- but simply to promote growth. In both situations, this is "overprescribing" of a very different sort.

There appears to be universal agreement on yet another point: The key to reducing antibiotic resistance is to reduce the use of antibiotics.

The Food and Drug Administration recently announced one approach for achieving this goal with respect to animals. In June, the agency issued draft guidance which recommends that antibiotics not be given to animals to promote growth and that when these drugs are used, they should be administered only under the supervision of a veterinarian. This is a good first step.

But we must do more to tackle this piece of the antibiotic resistance puzzle. And we must do so as part of a comprehensive strategy designed to safeguard the vitally important public health tool that is our antibiotics.

It is critical that we encourage the development of new drugs. But it also essential to preserve the antibiotics we already have. That means we must move expeditiously to slow the advancement of antibiotic resistance in both humans and animals.

In each instance, our strategy must be based on science. And the scientific evidence is now strong enough to create consensus among major public health groups and experts around the world that the time has come to reduce the use of antibiotics in animals. Organizations as diverse as the American Medical Association, the Institute of Medicine, the World Health Organization, and as we will hear from both CDC and the FDA, all agree: We must take action now.

Which brings us to today's hearing. We will have before us authorities from all sides of the antibiotics in animals debate – government officials, professionals in human and animal medicine, public health experts, drug industry representatives, and researchers. I encourage all Subcommittee members to join in sorting through the many views we will listen to today to see if we can identify an appropriate science-based policy to include as part of a comprehensive plan for addressing this rising public health emergency.

Let me thank all of our witnesses in advance of their testimony for their participation in today's hearing. We very much appreciate your time and interest and look forward to hearing from you.

Mr. WAXMAN. Can I ask, Mr. Chairman, two statements by unanimous consent be added to the record, one from two California-based groups, the San Francisco Medical Society and Physicians for Social Responsibility in L.A. regarding the use of antibiotics for animals?

Mr. PALLONE. Mr. Chairman, the——

Mr. WAXMAN. I ask unanimous consent their statements be added to the record.

Mr. PALLONE. The Republicans just want to look at it.

Mr. WAXMAN. I certainly want them to look at it. Whether they agree with the statements or not, I think that the groups——

Mr. SHIMKUS. Reserving the right to object. We don't want to get into——

Mr. WAXMAN. I will pull back and have you look at it, and then we will ask unanimous consent at a later time.

Mr. SHIMKUS. Thank you, Mr. Chairman.

Mr. PALLONE. OK. So we are going to proceed without at this point. I don't know, you took me back when you talked about seeing him on the beaches. I didn't realize you traveled from beach to beach.

Mr. WAXMAN. I was in L.A. My district has a lot of beaches and I didn't see him at any of them.

Mr. PALLONE. Next is the gentleman from Indiana. Oh you want to reserve your time. OK.

Then we go to the gentleman from Pennsylvania, Mr. Pitts.

OPENING STATEMENT OF HON. JOSEPH R. PITTS, A REPRESENTATIVE IN CONGRESS FROM THE COMMONWEALTH OF PENNSYLVANIA

Mr. PITTS. Thank you, Mr. Chairman.

This is now the third hearing this subcommittee has held on antibiotic resistance. First was on April 28th of this year and second was held on June 9th. There is no doubt that over the last 50 years antibiotics have saved countless lives worldwide. There is also no doubt that we are experiencing a growing amount of bacterial resistance to antibiotics, and many infectious diseases are becoming increasingly difficult to treat as a result.

For the purposes of this hearing, however, the key question is this: Does the use of antibiotics in feed-producing animals cause antibiotic resistance in humans? An exchange between Chairman Emeritus Dingell and Dr. Thomas Frieden, director of the Centers for Disease Control and Prevention, during the April 28th subcommittee hearing is instructive, and I will briefly quote. Mr. Dingell asked, "There appears to be much debate over whether the practice of adding antibiotics to agricultural feed is thought to promote drug resistance. What does current science and surveillance tell us on this point?" Dr. Frieden answered, "I am not aware of evidence in this country that has documented the spread from animals to humans, feed animals to humans." Mr. Dingell then replied, "I am getting the impression from what you are telling us here is that we really don't know what the nexus between the feed with antibiotics is and when there is a point of danger and what is the level of danger and what research is going on." Mr. Dingell was right. There is much that we don't know about how the use

of antibiotics in animals causes or does not cause antibiotic resistance in humans.

Clearly, more study must be done. However, until we have definitive scientific evidence, it seems to me that legislation like H.R. 1549, the Preservation of Antibiotics for Medical Treatment Act, or PAMTA, as they are calling it, which seeks to eliminate the use of antibiotics in animals except for treatment purposes, is premature and potentially dangerous. I am pleased that it appears that the FDA is working with the scientific and medical community in its new guidance, and I am interested to see what the comment period produces. As I have said before, we should study and explore every possible cause of antibiotic resistance but we should let the scientific evidence guide us.

I look forward to hearing from our distinguished panel of witnesses today. Thank you, Mr. Chairman. I yield back.

Mr. PALLONE. Thank you.

The gentlewoman from Illinois, Ms. Schakowsky.

OPENING STATEMENT OF HON. JANICE D. SCHAKOWSKY, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF ILLINOIS

Ms. SCHAKOWSKY. Thank you, Mr. Chairman, for your leadership on this issue.

The CDC has described antibiotic resistance as one of the world's most pressing health problems and overwhelming data proves that antibiotic resistance is increasing in this country. This is a safety issue, a public health issue and quite frankly an issue of national security.

Mr. Chairman, I would like to submit for the record statements regarding the need for legislative action to protect the effectiveness of antibiotics, legislation like the Preservation of Antibiotics for Medical Treatment Act. These letters are from organizations including the American Medical Association, the American Academy of Pediatrics, Consumers Union, Union of Concerned Scientists, and over 1,000 individual physicians from across the country who have concluded that the non-judicious use of antibiotics in livestock is a problem of public health. So if I could submit these for the record?

Mr. SHIMKUS. Reserving the right to object, Mr. Chairman, just so we get a chance to look at them.

Ms. SCHAKOWSKY. On June 28th, the FDA released draft guidance on this issue. The report states that "The overall weight of evidence supports the conclusion that using medically important antimicrobial drugs for production or growth-enhancing purposes in food-producing animals is not in the interests of protecting and promoting the public health." In other words, pumping animals full of non-medically necessary antibiotics is not good for public safety. I want to point out that this guidance carries no enforcement mechanism but rather asks the industry to voluntarily follow these suggestions.

It is obvious to me that legislation is needed. Eighty percent of the meet randomly tested by the National Antimicrobial Resistance Monitoring System shows traces of antibiotic-resistant bacteria. Antibiotic resistance is not a victimless phenomenon. Seventy per-

cent of the 98,000 people a year who die from hospital-related infections had a microbe resistance to one or more antibiotics.

Mr. Chairman, I have looked forward to this hearing for quite some time because it provides an opportunity to get the facts straight. I want to leave today knowing who has clear jurisdiction over the use of antibiotics in feed. If it is more than one agency, I want to know what the agencies are doing to work together and who is in the lead, and I want to feel confident that the agencies do not forget about this issue once this hearing is gaveled to a close, and I yield back.

Mr. PALLONE. Thank you.

Next is the gentlewoman from Tennessee, Ms. Blackburn.

OPENING STATEMENT OF HON. MARSHA BLACKBURN, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF TENNESSEE

Mrs. BLACKBURN. Thank you, Mr. Chairman, and thank you to those of you who prepared testimony and are here before us today. Certainly this is a topic that all of us are concerned about. Whether or not it should be the topic that is taking the time that we have today and the taxpayers' money, I will add, is a subject of another debate.

And Mr. Chairman, I will have to tell you, as we look at what is rolling out with this new health care law, I think it is very evident to us that that is where our time needs to be spent. When my children were little, and there was an issue in front of them that needed to be addressed, I would always remind them that avoiding the issue did not make it easier to handle the issue in the long term. If you want to address the problem, it is important that you hit it head on, and we are hearing from people of the numerous problems that exist with this health care bill that has been passed by this Congress and signed into law. There is a lot of concern over there over the expansion of agencies. There is tremendous confusion over the implementation or the expected implementation of that bill. There is surprise by taxpayers that benefits are going to be W–2'd back to them on their health insurance. We are hearing from employers all during the July 4th break as we talked about freedom and the imperative of preserving freedom. We heard from employers who were saying we are so concerned about the cost. Look at what it is going to cost us to provide insurance under this new list of mandates with all of these new agencies, with all of these new directives. That, believe it or not, translates into jobs lost, and the employers are concerned about that. Now, maybe my colleagues across the aisle are not that concerned but I can tell you losing the number of jobs that have been lost in the past 15 months is a tremendous concern. There is talk about rationing. There was a recess appointment. Talk about national security. How about securing the border? That is something that needs attention from this Congress. Definitely that is an issue that is of great importance to the American people.

Now, while the use of antibiotics in animals and the transference of that to humans is important and we are concerned, we know that there is a lack of large amounts of data on this issue. Does it need our attention? Yes. Do we need to keep a focus on this as

we go forward? Yes. But what is an imperative right now is that we look at what the people of this country are saying they want us to address, an ill-conceived health care bill that was passed that is a government takeover of health care and they want to make certain that we tend to getting that off the books. I yield back.

Mr. PALLONE. Next is the gentleman from Connecticut, Mr. Murphy.

Mr. MURPHY OF CONNECTICUT. Thank you, Mr. Chairman. I am eager to hear more about the subject that we are convened to learn about today, so I will waive my opening statement.

Mr. PALLONE. The gentleman from Georgia, Mr. Gingrey.

OPENING STATEMENT OF HON. PHIL GINGREY, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF GEORGIA

Mr. GINGREY. Mr. Chairman, thank you.

As past hearings have highlighted, we have a potential antibiotic crisis on the horizon. Simply put, we do not have enough new antibiotics in the development pipeline to meet the health care needs of the 21st century. Therefore, I believe it is important for this committee to review the current regulatory structure and promote incentives that will encourage greater antibiotic production. To that end, I look forward to working with my colleagues on both sides of the aisle to achieve this worthy goal and to look forward to the testimony, of course, from our witnesses today.

Mr. Chairman, on another note, following up a little bit from the opening statement of Ms. Blackburn, I am appalled that President Obama used the July 4th recess to appoint Dr. Donald Berwick as the new CMS administrator without allowing a single public hearing. During the health reform debate, this Administration promised the American people that reform would not ration health care. In fact, the White House's own Web site under the heading "health insurance reform reality check" claims to debunk, and I quote, "the myth that reform will mean a government takeover of health care or lead to rationing." According to Dr. Berwick, however, the question, and this is his quote, "is not whether or not we will ration care but whether we will do so with our eyes open." To be frank, Dr. Berwick's outspoken support of health care rationing is completely at odds with the Obama Administration's statements on whether rationing is good for our country.

In his inaugural address, President Obama said that, and I quote, "On this day, we gather because we have chosen hope over fear, unity of purpose over conflict and discord." In the July 26, 2008, edition of the British Medical Journal, Dr. Berwick chose hope when describing his support for the British health care rationing system and this is another quote from Dr. Berwick: "The only sentiment I feel for the NHS [National Health Service] that exceeds my admiration is my hope. I hope you will never, ever give up on what you have begun." Mr. Chairman, my hope is that we have some clarity on this issue. Either the President and his Administration support or they are opposed to health care rationing. The American people deserve answers, and unfortunately, this recess appointment has stolen those answers from them.

Mr. Chairman, I urge this committee to schedule a public hearing on Dr. Berwick and his plans for our seniors' health care pro-

gram. Further, given past statements and opposition to rationing, I believe that the Administration owes us answers to very, very simple questions. Number one: Does President Obama support Dr. Berwick's philosophy on health care rationing, and number two, does President Obama agree with Dr. Berwick's statement that any humane civilization must, again, Dr. Berwick "redistribute wealth from the richer among us to the poor and the less fortunate." Given that Dr. Berwick now runs our seniors' health care program, I sincerely believe the American people deserve a public hearing so we can get answers to these questions, and with that, Mr. Chairman, I will yield back.

Mr. PALLONE. The gentlewoman from the Virgin Islands, Ms. Christensen.

OPENING STATEMENT OF HON. DONNA M. CHRISTENSEN, A REPRESENTATIVE IN CONGRESS FROM THE VIRGIN ISLANDS

Mrs. CHRISTENSEN. Thank you, Mr. Chairman.

For decades, the scientific literature worldwide has shown that non-therapeutic low-dose antibiotic use in farm animals has caused increased resistance in humans yet I understand that in 1977 when FDA attempted to take steps to curtail such use, Congress ignored the research and the effort was lost. So thank you, Chairman Pallone and Ranking Member Shimkus for your attention to this important issue. Under your leadership, I am sure that we are not going to repeat that unfortunate interception, which is resulting in what is now termed a crisis in antibiotic resistance.

I commend the FDA for the draft guidance they have issued this year, and while I think it is a good first step, I think it is up to the Congress to go further and pass H.R. 1449, the Preservation of Antibiotics for Medical Treatment Act. Led by Denmark and Europe, it has been proven that good animal husbandry and judicious use of antibiotics has successfully reduced resistance without adversely affecting industry or profits. This is yet another area where our country is threatening to fall behind, and this is unacceptable, not only in terms of our leadership but because it places Americans at undue and unnecessary risk. It also has the potential to put our meat and poultry industry at risk. There can be no denying that swift and definitive action must be taken to protect the health of current and future generations as well as to protect the health of our future economy.

I welcome the witnesses and look forward to their testimony.

Mr. PALLONE. Thank you, Ms. Christensen.

I have two statements that Mr. Waxman put forward for the record, one from the San Francisco Medical Society and Physicians for Social Responsibility in—well, one from the San Francisco Medical Society, the other from the Physicians for Social Responsibility in Los Angeles regarding the use of antibiotics, and I would ask unanimous consent that these statements be entered into the record. Without objection, so ordered.

[The information appears at the conclusion of the hearing.]

Mr. PALLONE. And then we had another statement from Ms. Schakowsky. There were one or two letters from Ms. Schakowsky that she asked to be entered into the record, and I would ask unan-

imous consent that those also be entered into the record. Without objection, so ordered.

[The information appears at the conclusion of the hearing.]

Mr. PALLONE. And next is the gentleman from Michigan, our chairman emeritus, Mr. Dingell.

OPENING STATEMENT OF HON. JOHN D. DINGELL, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF MICHIGAN

Mr. DINGELL. Mr. Chairman, I thank you for your courtesy and I commend you for the hearing.

Today's hearing is the third in a series of hearings on the emerging public health threat posed by antibiotic resistance. The specific focus of this hearing has proven to be the more controversial aspect of the concern raised by public health experts. Its controversy spends decades and very frankly some very serious and important answers are required.

I introduced legislation on this topic in 1980, the Antibiotics Preservation Act. That bill would have directed the Secretary to designate antibiotic drugs which may or may not be used in subtherapeutic doses in animal feed or ingredients of animal feed unless such use is required to meet a compelling need. Interested parties expressed very passionate opinion on the legislation during hearings that year. I remember being troubled by the efforts of FDA Commissioner von Eschenbach in 2007 to approve use of certain antibiotics of last resort in food-producing animals. While there is substantial disagreement between major parties on the magnitude of the problem and the proper approach, I believe all sides would generally agree on two things. One, antibiotic resistance is a growing public health threat. According to the Infectious Diseases Society of America, about 2 million people across bacterial infections in U.S. hospitals each year. Ninety thousand people die as a result. About 70 percent of these infections are resistant to at least one drug.

It appears the injudicious use of medically important antimicrobial drugs in animal agriculture increases the level of antimicrobial resistance in animals and humans. A variety of scientific committees, task forces and organizations including a number of government organizations have studied the issue. The general conclusion drawn from these studies is that the injudicious use of antimicrobial drugs is not in the interest of protecting and promoting human health, and while that includes many different things, it is a warning to us.

While we can agree on these two points, there is a great deal of uncertainty as to how to address this critical issue and getting proper information on this matter is necessary to properly address it. We must not take for granted the current authority that rests in the Food and Drug Administration to responsively address this matter. I was encouraged by recent actions in that agency, specifically the issuance of a draft guidance, and look forward to updated programs in their work in other areas including the development of new antimicrobials.

I hope today's hearing will provide some interest on a few critical questions that come to my mind. First, is the problem best solved

by a one-size-fits-all approach or should the impact of each drug be separately considered? Two, are additional authorities and resources justifiably needed to fully address the problem? I might just observe, I think so. Three, do the benefits of curbing the use of antimicrobial drugs outweigh the risk of doing so? Four, what data should be reasonably required of regulators to justify future action on the use of antimicrobials in animal feed? And lastly, how do we define judicious use in a way that removes all ambiguity and helps us attain our public health goals while not impairing our other concerns about animal health and about the business of agriculture? I believe the answers to these questions will guide us as we seek ways to address the problem we have before us. Our attempt to address the problem should not be rushed. It must be based on sound science and good information. It must be done in a way that protects both human and animal health, and it should not unnecessarily disrupt the animal agricultural community.

I look forward to hearing the views and thoughts of our witnesses this afternoon. I am especially interested in hearing the views of our agency experts on this matter.

Again, Mr. Chairman, I thank you for this and I commend you for your leadership. I yield back the balance of my time.

Mr. PALLONE. Thank you, Chairman Dingell.

Next for an opening statement, the gentleman from Pennsylvania, Mr. Murphy.

OPENING STATEMENT OF HON. TIM MURPHY, A REPRESENTATIVE IN CONGRESS FROM THE COMMONWEALTH OF PENNSYLVANIA

Mr. MURPHY OF PENNSYLVANIA. Thank you, Mr. Chairman, for holding this hearing.

For decades, doctors have known that the widespread use of antibiotics is going to speed the development of bacterial mutation in antimicrobial resistance but what we don't do is give antibiotics to every schoolchild just to prevent infection.

Today, 70 percent of all health care-associated infections in the United States are resistant to at least one antibiotic. These infections cost some $50 billion a year. One antibiotic-resistant infection, MRSA, kills more people in the United States every year than HIV/AIDS. But what would happen if it finally becomes resistant to the few remaining effective antibiotics?

Of course, this resistance is not limited to human health. The vast majority of evidence for the last three decades points to linkage between routine low-level antibiotic use in food animals and the transfer of antibiotic-resistant bacteria to people, often through the food supply. The American Medical Association, the American Academy of Pediatrics, the American Public Health Association and the American College of Preventive Medicine have all called for a significant reduction in the amount of antibiotics we use in food animal production. Antibiotics have four purposes: to treat disease, control the spread of disease once an infection has occurred, prevent disease from occurring and promote the growth in animals.

Last month, the FDA issued guidance to drug makers, animal farmers, veterinarians that represents a step toward ending antibiotic use for growth promotion and increasing veterinary oversight

of animal antimicrobial drugs that are available over the counter at feed mills. Some drug makers are already moving in this direction, and I encourage pharmaceutical companies, farmers and the FDA to keep working together to limit any unnecessary use of antibiotics.

I look forward to hearing from the FDA and other witnesses of how they intend to ensure that disease prevention does not become growth promotion by another name. There are other solutions out there that will keep our food supply safe, our society healthy and our antibiotics effective, and I hope this hearing today will awaken our colleagues to the very real threat to public health posed by the declining effectiveness of antibiotics. Any use of antibiotics anywhere can cause bacteria to select for resistance but overuse and misuse of antibiotics simply gives bacteria an environment-rich situation to develop resistance and multiply.

To really cut health care costs, save lives and preserve the effectiveness of these vital drugs, we have to eliminate unnecessary antibiotic use everywhere we find it, in hospitals, nursing homes, the general community and sometimes even on the farm.

With that, I yield back.

Mr. PALLONE. Thank you, Mr. Murphy.

The gentleman from Ohio, Mr. Space.

OPENING STATEMENT OF HON. ZACHARY T. SPACE, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF OHIO

Mr. SPACE. Thank you, Mr. Chairman.

We have before us a public health issue of significant importance. Studies have indicated the antibiotics upon which our doctors and hospitals relied are losing their effectiveness in treating very serious illnesses. This resistance is a very real problem and indeed a very scary one. Our committee is right to investigate it and right to consider potential solutions.

I am, however, worried about some of the discussions relating to limiting the use of antibiotics in the agricultural setting. My Congressional district is home to a significant agricultural industry which directly employs over 17,000 people and countless more indirectly. It is the linchpin of our economy and an industry easily affected by regulation here in Washington, D.C. Many of the farmers in my district rely on the use of antibiotics to keep animal populations healthy and run productive businesses. And while we must be mindful of the importance of equipping farmers and veterinarians with the tools they need to treat animals when they are sick, obviously we all have to be mindful of the strategic necessary of preventing illnesses from spreading.

Today's witnesses offer a variety of opinions on this issue, many of which take different approaches to the same issue. I look forward to the testimony and to learning more about their perspectives. I believe it is critical that we study the evidence further and take into account all options and all sides of the issue before deciding whether to move forward. If the committee does decide to move forward on this issue, it is my hope we will move in a moderate and bipartisan fashion while working with stakeholders in the agricultural industry. This issue is an important one and worthy of

careful consideration, and we must be vigilant in ensuring that the policies we create are carefully thought out.

And with that, Mr. Chairman, I yield back.

Mr. PALLONE. Thank you, Mr. Space.

The gentleman from Iowa, Mr. Braley.

OPENING STATEMENT OF HON. BRUCE L. BRALEY, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF IOWA

Mr. BRALEY. Thank you, Chairman, for holding this important hearing on the use of antibiotics in animal agriculture, and I also want to thank all the witnesses who came here today, and I hope that we can have a meaningful conversation on this issue.

Most Americans when they go into a supermarket and buy some pork or chicken or beef have no idea where that food came from how or how it wound up in the supermarket or in their kitchen. A lot of public health officials have never been to a farm and seen with their own eyes and talked to production people involved in agriculture about how that food is taken care of and how it is grown and how it is processed and how it is shipped off to the packing house where it is ultimately dealt with and sent to their table.

A lot of parents take their kids into doctors' offices and demand the use of antibiotics for something that won't even respond because it is a viral infection. We are a culture that looks for simple, easy answers when oftentimes we are talking about complex tradeoffs, and it is no different here talking about the very real public health concerns about antibiotic resistance and very real production concerns about food safety and food supply.

When I was a student at Iowa State University, it was a well-known accepted fact that it was more difficult to get into the Iowa State Veterinary Medicine College than the University of Iowa College of Medicine, and yet we seem to think that public health research is somehow in some way more superior than animal veterinary research even though oftentimes they come from the same raw data.

So my hope for this hearing is that we can all agree on some fundamental things: A, that antibiotics are essential for fighting bacterial infections in humans, and yet there is still significant disagreement in some sectors about the specific relationship between the use of antibiotics in feed products as they relate to consumption of food and how that affects antibiotic resistance in humans. I have always been an advocate for science-based approach and I think this is an issue that demands careful, thoughtful consideration of all scientific points of view. Rather than come to conclusions based upon ideology, I think we need to look through the entire body of research available. There many well-intentioned people on both sides of this debate, and my hope is, we can continue to have meaningful discussions around tables like this, talk about the best forward to move forward to make sure we continue to have a safe, reliable food supply and are doing everything we can to protect human health. We need to continue to assess how antibiotics are being used in animals but also across the spectrum in ways that they are being abused and creating the type of antimicrobial resistance we are seeing today, and we also need to make sure that as we listen and learn from the witnesses who have come here today,

we continue to fund the necessary research to get to the bottom of how these problems relate to one another and how we make the best informed decisions to protect the public health interest.

So I want to thank you all for being here today. I look forward to your input, and I yield back.

[The prepared statement of Mr. Braley follows:]

July 14, 2010

Congressman Bruce Braley
Opening Statement

House Energy & Commerce Subcommittee on Health
Hearing on "Antibiotic Resistance and the Use of Antibiotics in Animal Agriculture"

Thank you Chairman Pallone, and thank you for holding this hearing on the use of antibiotics in animal agriculture. I would also like to thank the witnesses who came here today and hope that we can have a meaningful conversation on this issue.

I think we can all agree that antibiotics are essential for fighting bacterial infections in humans, but there is wide disagreement on how antibiotics use in animals could impact antibiotic resistance in humans.

I have long been an advocate of a science-based approach, and this case is no exception. Rather than come

to conclusions based on ideology, I think we need to take a thorough look at the entire body of research available on this subject.

There are plenty of well-intentioned people on both sides of this debate. It is my hope that we can continue to get all parties to come to the table and talk about the best way to move forward to make sure we continue to have a safe, reliable food supply and are doing everything we can to protect human health.

We must continue to assess how antibiotics are being used in animals, but recognize that there is a role for the judicious use of these antibiotics.

I look forward to hearing from our witnesses today and believe we need to continue researching and evaluating this public interest issue.

Thank you, Mr. Chairman, for taking up this important issue, and thank you to the witnesses for coming in today.

Mr. PALLONE. Thank you.

And we also have the gentleman from Georgia, Mr. Barrow.

Mr. BARROW. I thank the chairman.

I can add nothing to the comprehensive statement of my colleague, Mr. Braley, so I will waive an opening.

Mr. PALLONE. I thank the gentlewoman.

That concludes our opening statements so we will now turn to our first panel. I want to welcome you. Let me introduce each of you. First on my left is Dr. Joshua Sharfstein, who is the Principal Deputy Commissioner for the Food and Drug Administration. And then we have Dr. John Clifford, who is Deputy Administrator for Veterinary Services, Animal and Plant Health Inspection Service for the Department of Agriculture, and finally is Rear Admiral Ali Khan, who is Assistant Surgeon General, Acting Deputy Director of the National Center for Emerging and Zoonotic Infectious Disease with the Centers for Disease Control.

I think you know the drill, 5-minute opening statements. And I should mention, I guess we are expecting votes, but I am going to proceed and then we will see. We may have to—well, we will have to interrupt at some point but I think we might as well start with Dr. Sharfstein.

STATEMENTS OF JOSHUA SHARFSTEIN, M.D., PRINCIPAL DEPUTY COMMISSIONER, FOOD AND DRUG ADMINISTRATION, U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES; JOHN CLIFFORD, D.V.M., DEPUTY ADMINISTRATOR, VETERINARY SERVICES, ANIMAL AND PLANT HEALTH INSPECTION SERVICE, U.S. DEPARTMENT OF AGRICULTURE; AND REAR ADMIRAL ALI S. KHAN, M.D., M.P.H., ASSISTANT SURGEON GENERAL, ACTING DEPUTY DIRECTOR, NATIONAL CENTER FOR EMERGING AND ZOONOTIC INFECTIOUS DISEASE, CENTERS FOR DISEASE CONTROL AND PREVENTION, U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

STATEMENT OF JOSHUA SHARFSTEIN

Dr. SHARFSTEIN. Good afternoon, Chairman Pallone and Ranking Member Shimkus and members of the subcommittee. I am Dr. Joshua Sharfstein, Principal Deputy Commissioner of the Food and Drug Administration, an agency of the Department of Health and Human Services. Thank you for holding this hearing. Thank you for the opportunity to discuss FDA's role and work with respect to antimicrobial resistance, and we appreciate your leadership.

In my testimony, I will describe FDA's actions to combat resistance and discuss the newly released draft guidance entitled "The Judicious use of medically important antimicrobial drugs in food-producing animals."

As I will discuss in more detail later, in the draft guidance FDA concludes that the overall weight of evidence to date supports the conclusion that using medically important antimicrobial drugs for production purposes is not in the interest of protecting and promoting the public health. Developing strategies for reducing antimicrobial resistance is critically important for protecting both human and animal health, both of which are very important to scientists and regulators at the FDA.

Antimicrobial resistance is being addressed on a number of fronts. Dr. Khan from CDC will talk about the data associated with human resistance as it relates to antimicrobial use, and his agency's leadership in efforts to fight resistance in human medicine, but I do want to make a comment as a pediatrician.

I remember vividly in 1998 when I was a pediatric resident and the Centers for Disease Control and the American Academy of Pediatrics published principles for the judicious use of antibiotics in common pediatric infections including the common cold, ear infections, sinusitis and sore throat. I remember giving conferences on the basis of that and I remember the format of the papers and how they printed off the computer. Children have many infections, and as Congressman Braley mentioned, there was a big issue of parents coming and expecting antibiotics, and these were very strict guidelines for pediatrics on when to use antibiotics and when not to. There was a major effort in pediatrics starting around that time to reduce prescribing, to reduce antimicrobial resistance, and it had an impact. A recent study in the Journal of the American Medical Association showed that antibiotic prescription rates for children under 5 with respiratory infections decreased by 41 percent between 1995 and 2005. That study was published last year.

Many centers at FDA are addressing the public health concern about antimicrobial resistance including the Device Center, which works on diagnostics, the Biologic Center, which works on vaccines, the Drug Center, which works on Drugs. Because today's hearing focuses on antimicrobials in agriculture, I want to talk about the efforts at the Center for Veterinary Medicine.

Our efforts start with surveillance through the National Antimicrobial Resistance Monitoring System. CVM works with CDC and USDA in overseeing surveillance of resistance in multiple areas. In addition, CVM has an approach for assessing resistance associated with the use of drugs intended for food-producing animals. There was a guidance issued, Guidance 152, which explains an approach when there is a new product coming onto the market, how we assess whether there is a risk from antimicrobial resistance and how that translates into our regulatory pathway.

However, many antimicrobial drug products that were approved prior to the implementation of this guidance have not been evaluated, and a particular concern are those antimicrobials that are considered medically important drugs, meaning those that are important in human medicine and are approved in food-producing animals for production or growth-enhancing purposes.

To address this concern, the Center for Veterinary Medicine released a guidance, as you have heard, on June 28. This is intended to inform the public of FDA's thinking on this issue and to minimize resistance by outlining broad principles for assuring that medically important antimicrobial drugs are used judiciously in animal agriculture. The draft guidance reviews major public health reports on this topic including reports by the Institute of Medicine, the Government Accountability Office, the World Health Organization and its affiliated agencies. Those reports include multiple peer-reviewed studies conducted around the world including in the United States.

Based on this evidence, in this draft guidance FDA recommends phasing-in measures that would, one, limit medically important antimicrobial drugs to uses in food-producing animals that are considered necessary for assuring animal health, and two, include veterinary oversight or consultation. These steps would help reduce overall use of medically important antimicrobial drugs and reduce the selection pressure that generates antimicrobial resistance.

Prior to issuing the draft guidance, FDA consulted with a wide variety of stakeholders. We spoke with CDC and USDA and got their input on the recommendations. I visited a farm in southern Illinois, which was a very interesting experience, and we are committed to working with all stakeholders across the spectrum, our sister agencies as we get comments from the public on the right way to implement this policy. We are seeking comment through August 30, 2010, and we look forward to a very productive dialog to figure out a very sensible path through this issue that promotes both human and animal health. Thank you.

[The prepared statement of Dr. Sharfstein follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

STATEMENT OF

JOSHUA M. SHARFSTEIN, M.D.

PRINCIPAL DEPUTY COMMISSIONER

FOOD AND DRUG ADMINISTRATION

DEPARTMENT OF HEALTH AND HUMAN SERVICES

BEFORE THE

SUBCOMMITTEE ON HEALTH

COMMITTEE ON ENERGY AND COMMERCE

UNITED STATES HOUSE OF REPRESENTATIVES

JULY 14, 2010

RELEASE ONLY UPON DELIVERY

INTRODUCTION

Good afternoon, Chairman Pallone and Members of the Subcommittee, I am Dr. Joshua M. Sharfstein, Principal Deputy Commissioner of the Food and Drug Administration (FDA or the Agency), which is an agency of the Department of Health and Human Services (HHS). Thank you for the opportunity to discuss FDA's role with regard to antimicrobial resistance. We appreciate your leadership on this important public health matter.

Preserving the effectiveness of current antimicrobials and encouraging the continued development of new ones, are vital to protecting human and animal health against infectious microbial pathogens. A 2004 report from the Infectious Diseases Society of America (IDSA) noted that "About two million people acquire bacterial infections in U.S. hospitals each year, and 90,000 die as a result. About 70 percent of those infections are resistant to at least one drug." Resistant pathogens lead to higher health care costs because they often require more expensive drugs and extended hospital stays. The problem is not limited to hospitals. Clinicians practicing in every field of medicine, including my own field of pediatrics, encounter resistant infections frequently. So, too, do veterinarians. Community-acquired infections are frequently resistant to multiple antimicrobial drugs, such as community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA), common respiratory pathogens including *Streptococcus pneumoniae*, and gram-negative bacilli, which can infect humans through contaminated food.

In my testimony, I will provide background information on antimicrobial resistance, describe FDA's actions to combat resistance and promote product development, and discuss the newly released draft guidance entitled, "The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals."

As I will discuss in more detail later, in the draft guidance, FDA concludes that the overall weight of evidence available to date supports the conclusion that using medically important antimicrobial drugs for production purposes is not in the interest of protecting and promoting the public health. Developing strategies for reducing antimicrobial resistance is critically important for protecting both public and animal health.

BACKGROUND

Antimicrobial drugs are used to treat infections caused by microorganisms. The term "antimicrobial" refers broadly to drugs with activity against a variety of microorganisms including bacteria, viruses, fungi, and parasites (such as malaria). The term "antibacterial" refers to drugs with activity against bacteria in particular. Another term commonly used to describe an antibacterial drug is "antibiotic." This term refers to a natural compound produced by a fungus or another microorganism that kills bacteria that cause disease in humans or animals. Some antibacterial drugs are synthetic compounds; i.e., they are not produced by microorganisms. Though these do not meet the technical definition of antibiotics, they are referred to as antibiotics in common usage.

Antimicrobial resistance is the ability of bacteria or other microbes to resist the effects of a drug. Antimicrobial resistance occurs when bacteria change in some way that reduces or eliminates the effectiveness of drugs, chemicals, or other agents designed to cure or prevent infections.

Many factors contribute to the spread of antimicrobial resistance. In some cases, doctors prescribe antimicrobials too frequently or inappropriately. Sometimes patients do not complete the prescribed course of an antimicrobial, making it more likely that surviving microbes will develop resistance.

Antimicrobial use in animals contributes to the emergence of resistant microorganisms that can infect people. Through international trade and travel, resistant microbes can spread quickly worldwide.

Antimicrobial agents have been used in human and veterinary medicine for more than 50 years, with tremendous benefits to both human and animal health. Many infections that were fatal, or left individuals with severe disabilities, are now treatable or preventable. However, because resistance to antimicrobial drugs is expected to occur with their use, it is essential that such drugs be regulated and used judiciously to delay the development of resistance. Misuse and overuse of these drugs contribute to an even more rapid development of resistance. After several decades of successful antimicrobial use, we have seen and continue to see the emergence of multi-resistant bacterial pathogens, which are less responsive to therapy. Antimicrobial resistant bacterial populations are emerging because of the combined impact of the various uses of antimicrobial drugs, including their use in humans and animals.

New classes or modifications of older classes of antimicrobials over the past six decades have been matched slowly but surely by the development of new bacterial resistance mechanisms. As of today, antimicrobial resistance mechanisms have been reported in the scientific literature for all known antibacterial drugs that are currently available for clinical use in human and veterinary medicine. In some cases, strains have been isolated that are resistant to multiple antibacterial agents.

U.S. INTERAGENCY TASK FORCE ON ANTIMICROBIAL RESISTANCE

The U.S. Interagency Task Force on Antimicrobial Resistance (Task Force) was created in 1999 to develop a national plan to combat antimicrobial resistance. FDA co-chairs the Task Force, along with the Centers for Disease Control and Prevention (CDC) and the National Institutes of Health.

The Task Force also includes the Agency for Healthcare Research and Quality, Centers for Medicare and Medicaid Services, the Health Resources and Services Administration, the United States Department of Agriculture (USDA), the Department of Defense, the Department of Veterans Affairs, and the Environmental Protection Agency. In 2001, the U.S. Agency for International Development joined the Task Force to help address global antimicrobial resistance issues.

In 2001, the Task Force published the "Public Health Action Plan to Combat Antimicrobial Resistance" (Action Plan). The Action Plan has four major components: surveillance, prevention and control, research, and product development. The Interagency Task Force has been working on a revised Action Plan. The revised Action Plan, which is currently undergoing interagency review, will provide more specific action items than the 2001 Action Plan and will include goal dates for completing many of the action items.

ANTIBIOTIC REDUCTION IN HUMAN MEDICINE

The issue of antimicrobial resistance is being addressed on a number of fronts. My colleague from CDC will discuss the data associated with human resistance as it relates to antimicrobial

use in food-producing animals and on his agency's leadership in efforts to fight resistance in human medicine. As a pediatrician, I remember when CDC and the American Academy of Pediatrics published principles in 1998 (Dowell SF, Marcy SM, Phillips WR, Gerber MA, Schwartz, B. *Pediatrics*. 1998;101:163-165) for the judicious use of antibiotics in common pediatric infections: the common cold, otitis media, acute sinusitis, and pharyngitis. Children often have a high number (3-8) of viral upper respiratory infections each year and it is important to not be using antibiotics for viral infections which will not respond to them but will increase the child's probability of having a resistant organism when they do have an infection due to a bacteria. Otitis media, or ear infections, are one of the most common infections of childhood where an antibiotic may be needed. By three years of age, greater than 80% of children have had at least one episode of acute otitis media and 46% have had three or more episodes of ear infections. Judicious use of antibiotics helps decrease the probability that this common infection will be caused by an organism that is resistant to the more commonly used antibiotics (Feigin & Cherry: 1998). This initiative has been successful in reducing antibiotic prescription rates. Pediatricians are now using more discretion when administering antibiotics to their patients. A recent study in the Journal of the American Medical Association, which utilized national databases, reported that antibiotic prescription rates for children under five years of age with respiratory tract infections (including infections such as the common cold) decreased by 41% between 1995-1996 and 2005-2006 (JAMA 2009;302:758-66).

FDA'S ACTIVITIES TO COMBAT ANTIMICROBIAL RESISTANCE

Many Centers at FDA are addressing the public health concern about antimicrobial resistance. For example, research and regulatory efforts at the Center for Biologics Evaluation and Research (CBER) have contributed to the development and continued availability of effective vaccines

which have eliminated or markedly decreased antimicrobial resistance by reducing or nearly eliminating some types of infections. Additionally, the Center for Devices and Radiological Health (CDRH) leads several efforts to clarify regulatory requirements for both industry and the scientific community on clearance of diagnostic tests for use in antimicrobial resistance initiatives.

Since today's hearing focuses specifically on the use of antimicrobials in animal agriculture, my testimony will highlight the efforts at the Center for Veterinary Medicine (CVM). I will also provide a brief update to Dr. Janet Woodcock's recent testimony before this Subcommittee about the initiatives at the Center for Drug Evaluation and Research (CDER).

Center for Veterinary Medicine (CVM)

FDA's strategy for addressing the antimicrobial resistance issue starts with surveillance through the National Antimicrobial Resistance Monitoring System (NARMS). NARMS is a multi-faceted system that monitors trends in the prevalence of antimicrobial-resistance among bacteria isolated from humans, retail meats, and food animals. CVM is the lead coordinator of NARMS and collaborates with CDC, the United States Department of Agriculture's (USDA) Agricultural Research Service and State public health laboratories. NARMS data are critical for monitoring antimicrobial drug resistance among Salmonella and other enteric bacterial organisms from human and animal populations, as well as retail meats. Such data provide important information to regulatory officials, physicians, and veterinarians for assessing trends and identifying appropriate risk mitigating measures. Additionally, NARMS provides a national source of enteric bacterial isolates that are invaluable for conducting antimicrobial resistance research.

As part of the new animal drug approval process, CVM developed and implemented an approach for assessing antimicrobial resistance concerns associated with the use of antimicrobial drugs intended for use in food-producing animals. This approach uses risk assessment methodologies to assess the potential human health impact from the proposed antimicrobial use in animals and outlines risk management strategies that may be applied. In 2003, FDA published Guidance for Industry #152, "Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to their Microbiological Effects on Bacteria of Human Health Concern." (To view FDA guidance documents, please visit *http://www.fda.gov/RegulatoryInformation/Guidances/default.htm*). Guidance #152 provides recommendations to drug sponsors on the use of a qualitative risk assessment approach for evaluating the likelihood that an antimicrobial drug used to treat a food-producing animal may cause an antimicrobial resistance problem in humans. The risk assessment approach recommended in the guidance considers a broad set of information, including the importance of the drug in question to human medicine. This information is collectively considered in determining whether the proposed antimicrobial product will pose a risk to public health.

FDA believes the approach outlined in Guidance #152 for evaluating the safety of antimicrobial drugs as part of the drug approval process is scientifically sound and is protective of the public health. However, many antimicrobial drug products, approved prior to the implementation of Guidance #152 in 2003, have not been evaluated under the current processes for assessing safety with respect to antimicrobial resistance. Of particular concern are those antimicrobials that are considered medically important drugs (i.e., those drugs or classes of drugs that are important in human medicine) and are approved for use in food-producing animals for production or growth-enhancing purposes.

Judicious Use Guidance for Antimicrobials in Food-Producing Animals

To address this concern, CVM released a draft guidance on June 28, 2010, entitled, "The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals" *(http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM216936.pdf)*. This draft guidance is intended to inform the public of FDA's current thinking on the use of medically important antimicrobial drugs in food-producing animals. It is intended to help minimize antimicrobial resistance by outlining several broad principles for assuring that medically important antimicrobial drugs are used judiciously in animal agriculture.

The draft guidance reviews the major public health reports on this topic – including reports by the Institute of Medicine, the Government Accountability Office, and the World Health Organization. FDA believes the overall weight of evidence available to date supports the conclusion that using medically important antimicrobial drugs for production purposes is not in the interest of protecting and promoting the public health.

In the draft guidance, FDA recommends phasing in measures that would (1) limit medically important antimicrobial drugs to uses in food-producing animals that are considered necessary for assuring animal health and (2) include veterinary oversight or consultation. These steps would help reduce overall use of medically important antimicrobial drugs, thereby reducing the selection pressure that generates antimicrobial resistance. Prior to issuing the draft guidance, FDA consulted with USDA to seek their input on the recommendations. FDA and USDA are committed to working collaboratively to address this important public health issue.

FDA is seeking public comment on the draft guidance through August 30, 2010. FDA is committed to working with USDA, animal drug sponsors, the veterinary and public health communities, the animal agriculture community, and all other interested stakeholders in developing a strategy to address antimicrobial resistance concerns in a manner that is protective of both human and animal health. For example, FDA intends to work closely with USDA, producers, and veterinarians on strategies for increasing veterinary involvement in the use of antimicrobial drugs and for assuring that specific animal health needs are met as the measures outlined in the guidance are implemented.

Center for Drug Evaluation and Research (CDER)

FDA's efforts to address antimicrobial resistance are not limited to uses of antibiotics in food-producing animals. It is important that (1) our existing antibacterial drugs for humans be used prudently to preserve their effectiveness and (2) that new antibacterial drugs for humans be developed as we expect that resistance will develop to existing therapies over time. In her recent testimony, Dr. Woodcock described several initiatives under way to address challenges in human medicine at CDER, which include gathering scientific data to inform the development of recommendations on designing informative, ethical, and feasible clinical trials; issuing draft guidance documents concerning clinical trial designs for studying antibacterial drugs; and working towards publishing additional draft guidance documents in the coming months to address the development of antimicrobial drugs intended for use in treating skin infections and hospital-acquired/ventilator-associated bacterial pneumonia. In addition, FDA recently announced a public workshop to be held August 2-3, 2010, regarding issues in the design and conduct of clinical trials for antibacterial drug development. The public workshop is intended to provide information for and gain perspectives from health care providers, researchers, academia,

industry, and regulators on various aspects of design and conduct of clinical trials for antibacterial drugs.

CONCLUSION

Addressing antimicrobial resistance is a challenging task which requires the expertise and efforts of many entities. FDA will continue to work with Federal, State, local, and foreign government officials, medical professionals including the veterinary community, the regulated industry and all of FDA's stakeholders, in developing sound strategies to address and advance both human and animal health.

Thank you for the opportunity to discuss FDA's activities with regard to antimicrobial resistance. I would be happy to answer any questions.

Mr. PALLONE. Thank you, Dr. Sharfstein.
Dr. Clifford.

STATEMENT OF JOHN CLIFFORD

Dr. CLIFFORD. Good afternoon, Chairman Pallone and Ranking Member Shimkus and other members of the subcommittee. My name is Dr. John Clifford and I am the Deputy Administrator for Veterinary Services with the Department of Agriculture's Animal and Plant Health Inspection Service. In this position, I also serve as the U.S. Chief Veterinary Officer for animal health.

Today the subcommittee is looking at an important issue that has far-reaching consequences for human and animal health. USDA believes that it is likely that the use of antimicrobials in animal agriculture does lead to some cases of antimicrobial resistance among humans and in animals themselves, and we believe that we must use medically important antimicrobials judiciously. USDA is committed to playing an active role in preserving the effectiveness of medically important antimicrobials.

USDA believes that policy decisions must be science-based and will provide research to inform the debate. To do this, USDA will work with our federal partners including those at this table.

What constitutes judicious use and how it applies is a central question to this debate. This must be answered with a sound scientific evaluation and with data-based decision-making. USDA is working to conduct surveillance and research and a number of agencies within the Department are actively engaged on projects to better understand the issue. My written statement details many of these efforts.

Beyond my department, FDA has an existing process for completing risk assessments concerning the use of antimicrobials. USDA believes that this process provides a rational, science- and data-based approach to making decisions about specific antimicrobial use. This is preferable to the approach that broadly eliminates antimicrobials for specific uses.

As we move forward, we must carefully address what current research says and identify gaps in our scientific knowledge. We are committed to working with our federal partners as we have been on these important issues. We need more data so that the policy can properly balance risk between animal and human health needs.

USDA is also looking to expand its existing partnership. For instance, USDA is interested in expanding our work with HHS to improve outreach with veterinarians in the animal agriculture community. We need to work together to conduct research and develop new therapies that protect and preserve animal health without increasing the risk of resistance to medically important antimicrobials.

USDA is also interested in making our veterinary experts available to provide guidance and share information with veterinarians and producers. This Nation's farmers and ranchers want to do the right thing. If we provide them with the resources and information so they can make informed decisions, they will do the right thing.

Mr. Chairman, I can assure you that USDA recognizes the challenges of antimicrobial resistance and that the entire Department

is taking these challenges very seriously. We are committing to ensuring that medically important antimicrobials are used judiciously, which will preserve both human and animal health.

I will be happy to answer any questions that you or your members of the committee may have. Thank you.

[The prepared statement of Dr. Clifford follows:]

Testimony of Dr. John Clifford
Deputy Administrator for Veterinary Services
Animal and Plant Health Inspection Service
U.S. Department of Agriculture

Before the House Committee on Energy and Commerce's
Subcommittee on Health
Hearing on Antibiotic Use in Animal Agriculture
July 14, 2010

Mr. Chairman and Members of the Subcommittee, my name is Dr. John Clifford, and I am the Deputy Administrator for Veterinary Services with the Department of Agriculture's (USDA) Animal and Plant Health Inspection Service (APHIS). In this position, I also serve as USDA's Chief Veterinary Officer.

Today, the Subcommittee is looking at an important issue that has far-reaching consequences for both human and animal health. USDA believes that it is likely that the use of antibiotics in animal agriculture does lead to some cases of antibacterial resistance among humans and in the animals themselves and it is important that these medically important antibiotics be used judiciously.

USDA is committed to playing an active role in preserving the effectiveness of medically important antibiotics; in addition to ongoing research, we are committed to identifying opportunities to reduce usage and maintain the effectiveness of these drugs – whether through the development of new treatment options for animals, such as vaccines, or through outreach and education to this country's agricultural producers so that they have better information on antibiotic use.

USDA believes that decisions regarding the issue of antibiotic use must be science-based and is interested in providing the most current scientific information when it can, and collaborate with HHS' CDC, FDA, National Institutes of Health (NIH), and other Federal agencies on this important issue.

Several agencies within USDA are actively working to conduct surveillance and research on key issues related to antimicrobial resistance. Within USDA, APHIS, along with Agricultural Research Service (ARS), Food Safety and Inspection Service (FSIS), Economic Research Service (ERS), and National Agricultural Statistics Service (NASS) are actively engaged on a series of projects to better understand these issues. I have provided more information about these many ongoing projects in the Appendix at the end of this testimony.

CHALLENGES USDA FACES

Last month, FDA issued guidance on antimicrobial resistance. This guidance provides an opportunity to seek comments and find answers to many important questions. For instance, determining how to apply the concept of "judicious use" in the field will be critical. USDA

believes that making this type of determination must be based on sound scientific evaluation, and data-based decision making. USDA believes that animal health impacts must be considered in the context of the decision making process.

FDA, under its regulatory authority, has an existing process for completing risk assessments concerning the use of antimicrobials. USDA believes that this process provides a rational, science- and data-based approach to making decisions about specific antimicrobial use as opposed to an approach that broadly eliminates antimicrobials for specific uses.
In addition, we note that the ecology of antimicrobial resistance is very specific to its conditions, such as the characteristics of the bacterial organism itself and the patterns of antimicrobial use in human health settings and food production systems. It is also inextricably linked to other ecologic niches such as bacterial populations associated with wildlife, soils, waste disposal, etc. There are ebbs and flows between these niches, and these constant changes are important to consider within this context. These fluctuations may make it difficult to apply broad solutions to a variety of unique conditions. While USDA and its federal partners are conducting surveillance and research on antimicrobial resistance, we currently lack robust monitoring tools that would allow for an understanding of this ecology and the impact of proposed solutions.

To that end, we must carefully address what current research says, and identify gaps in our scientific knowledge. Antibiotics have been widely used in veterinary and human medicine for over half a century, and the benefits to the health of both is widely acknowledged. Research also shows that increased usage of some antimicrobial drugs likely does lead to resistance[1,2]. But how much and how quickly?

On the question of veterinary oversight and consultation, which was also included in the FDA guidance document, USDA believes it is important to consider the challenges due to the lack of large animal veterinarians in rural areas. Due to larger distances and traveling times in rural areas, it may be difficult for producers to consult with veterinarians on these types of decisions. USDA believes it is important to work together with Federal partners, veterinarians, and other stakeholders to find feasible solutions to implement this recommendation.

USDA'S ROLE GOING FORWARD

USDA is committed to continue partnering with other federal agencies to address these details and to find feasible solutions to some of the challenges. USDA is also looking to expand its existing partnerships. For instance, USDA is interested in expanding our work with HHS in identifying how to reduce antibiotic use through improved outreach and collaboration with veterinarians and the animal agriculture community. In addition, we believe that additional research should be pursued that explores whether alternatives to medically important antibiotics are available. We need to work together to conduct research and develop new therapies that protect and preserve animal health, without increasing the risk of resistance to medically

[1] Bonten et al. Vancomycin-resistant enterococci: why are they here, and where do they come from? *The Lancet Infectious Diseases* December 2001; 1(5): 314-325.
[2] Dutil et al. Certiofur Resistance in *Samonella enteric* Serovar Heidelberg from Chicken Meat and Humans, Canada. *Emerging Infectious Diseases* January 2010; 16(1): 48-54.

important antibiotics. Included in our efforts, we must identify alternative animal health management techniques – tools and technologies, including newer and better vaccines and diagnostic tests. That portion of the partnership would extend beyond our federal partners to farmers and producers themselves. USDA wants to partner with them to facilitate the judicious use of antibiotics in ways that are feasible to farmers and ranchers.

For instance, USDA is interested in making our veterinary experts available to provide guidance and share information with veterinarians and producers. In some rural areas, access to an experienced veterinarian is limited, especially when dealing with large animals. Given the larger distances in rural areas, we must do more to ensure that producers are receiving the assistance they need to make informed decisions about the use of antibiotics with their animals.

Mr. Chairman, I can assure you that USDA recognizes the challenges of antibiotic resistance, and that the entire Department is taking these challenges very seriously. We are committed to ensuring that medically important antibiotics are used judiciously, which will preserve both human and animal health. USDA already is and will continue to play an active role in preserving the effectiveness of those drugs. We are performing surveillance, conducting research, and increasing education. Together, those three facets will help protect American agriculture, while preserving the needs of human medicine.

APPENDIX: CURRENT USDA EFFORTS AND PARTNERSHIPS

Various USDA agencies are engaged in the research and analysis of antibiotic use and antimicrobial resistance to keep USDA at the forefront of maintaining a stable and healthy system of American agriculture. APHIS partners with other USDA agencies to include: Agricultural Research Service (ARS), Food Safety and Inspection Service (FSIS), Economic Research Service (ERS), and National Agricultural Statistics Service (NASS). We work together in various capacities to collect samples and data, develop diagnostic methods, and analyze data.

Beyond our partnerships within USDA, the Department also regularly collaborates with other federal agencies. Antibiotic resistance is a multi-faceted issue, and we have and continue to partner with agencies, such as the HHS' CDC, FDA, and NIH.

USDA is a member of the Interagency Task Force on Antimicrobial Resistance. The Task Force, which was created in 1999, is co-chaired by the CDC, FDA and NIH, and includes a broad range of federal partners. The Task Force developed a comprehensive document, *A Public Health Action Plan to Combat Antimicrobial Resistance*, which reflects a broad-based consensus of federal agencies on actions needed to address antimicrobial resistance. The Action Plan provides a blueprint for specific, coordinated federal actions to address the emerging threat of antimicrobial resistance.

In 2007, the Task Force held a public meeting, soliciting input to update the Action Plan. The revised Action Plan is undergoing agency clearance, after which time it will be available for public comment.

Also key to our efforts to address antimicrobial resistance is the National Antimicrobial Resistance Monitoring System (NARMS). NARMS was established in 1996 as a partnership of the FDA, ARS, FSIS, APHIS and CDC. The NARMS program monitors changes in antimicrobial drug susceptibilities of selected enteric bacterial organisms in humans, animals, and retail meats. The system is intended to provide meaningful data to help identify antimicrobial drug resistance in humans and animals, and to provide timely updates to veterinarians and physicians on patterns of resistance. It is part of the overall federal strategy to combat antimicrobial resistance that fulfills the need for a national surveillance program to monitor resistance among foodborne pathogens in humans and animals.

USDA supports NARMS through three of its agencies. FSIS contributes isolates from its regulatory program for Salmonella and isolates of Campylobacter from its microbiological baseline data collection surveys. APHIS has contributed isolates from clinically ill animals and from healthy animals on farms. And ARS conducts all testing and analysis of isolates collected by USDA. ARS reports the information it compiles yearly and shares this information and data on the Internet at: http://www.ars.usda.gov/Main/docs.htm?docid=6750. The impact of NARMS has been to assist the FDA in regulatory decision making on animal antimicrobial drugs, practitioners on prudent use practices, and commodity organizations on quality improvement.

In addition to these efforts, APHIS has been collecting an increasing amount of data on production practices and samples containing bacteria that have been used to evaluate levels and impacts of antimicrobial use on livestock operations throughout the United States. This data and the samples are collected through the National Animal Health Monitoring System (NAHMS), which conducts national studies on the health and health management of domestic livestock and poultry populations. Bacterial isolates gathered via NAHMS have been tested for antibiotic resistance and included in NARMS. The data collected yielded information on, among other things, the types of antimicrobials used to treat various common diseases in animal populations, how producers decide to treat and what to treat with, how antimicrobial drugs are delivered to the animals (via feed, water, or parenterally), and primary influencers on the antimicrobial drug decision-making process. All of these factors are critical to understanding how to optimize antimicrobial drug use in animal populations.

APHIS, in collaboration with ARS, has also been collecting samples to be cultured for bacteria as part of the NAHMS program, which are subsequently evaluated for antimicrobial drug resistance as part of the NARMS program. These studies provide information on the extent of antimicrobial drug resistance among potential foodborne pathogens and commensal organisms in livestock populations. Such information is critical to risk assessments that evaluate the potential for transfer of the resistant organism or resistance determinants through the food chain.

An additional step USDA is taking to better understand the complexities of this issue is through our work with the Codex ad hoc Intergovernmental Task Force on Antimicrobial Resistance. The Task Force was established by the 29th meeting of the Codex Alimentarius Commission. FDA is the lead agency for the U.S., serving as the Delegate. USDA's FSIS co-leads and is the Alternate Delegate.

The Task Force has a four-year timeline to produce a guidance document, which is expected to be complete in October 2010. The intent of this guidance is to assess the risks to human health associated with the presence and transmission of antimicrobial resistant microorganisms and antimicrobial resistance genes through food and feed, as well as to develop appropriate risk management advice based on that assessment to reduce such risk.

Mr. PALLONE. Thank you, Dr. Clifford.
Dr. Khan, or Admiral Khan, I guess.

STATEMENT OF ALI KHAN

Admiral KHAN. Good afternoon, Chairman Pallone, Ranking Member Shimkus and other members of the subcommittee. I am Ali Khan from CDC, and thank you for the invitation to address the subcommittee today.

Antimicrobial agents are used to treat infection by different disease-causing microorganisms. Resistance occurs whenever and wherever antibiotics are used, in the community, on the farm or in health care settings. Antibiotics are a subset of antimicrobials used specifically to fight bacterial infections. Many of the bacteria in our food that cause human disease are also in food animals. These healthy food-producing animals commonly carry bacteria in their intestinal tract and they can cause disease in humans including Salmonella and Campylobacter are two examples. Today I will focus on the human health impact of antibiotic-resistance bacteria as they relate to food animals.

There is unequivocal and compelling evidence that the use of antibiotics in animals leads to the development of drug-resistant bacteria that have adverse impacts on human public health. This has been demonstrated for numerous production animals—pigs, cattle, poultry—for numerous pathogens—Salmonella, E. coli, Campylobacter enterococcus—and in numerous countries—Denmark, England, Spain, Canada, and right here in the United States. Antibiotic-resistant pathogens move through the food supply, so use of antibiotics in animals results in resistant bacteria in food animals. These resistant bacteria then can be present in the food supply and be transmitted to humans. And finally, these resistant bacterial infections can result in adverse human health consequences such as increased hospitalizations or potentially death.

Please allow me to describe some specific examples. Let us see if slide one works here. Can somebody bring up the first slide potentially?

Mr. PALLONE. Do we have technicians here? Oh, there you go.

Admiral KHAN. Let us go to the next one. Perfect.

[Slide shown.]

So Campylobacter is one of the leading causes of foodborne bacterial disease in the United States. It causes approximately 2 million cases per year. And studies have unequivocally demonstrated movement of resistant pathogens through the food supply linked to antibiotic use in animals. So what you can see nicely in this slide to the far left is antibiotic—well, that depends on what side of the screen you are looking at, to the far left of the slide. There is probably less than 1 percent resistance in those bacteria, and then following the use of fluoroquinolones and the licensing for fluoroquinolones in poultry, what you can see is a dramatic increase starting 2 to 3 years later that has persisted despite a decision by FDA a couple of years ago to stop the use of fluoroquinolones.

Now, this failure to see a subsequent decline in resistance really is a cautionary tale for us and it suggests that the movement of resistance from animals to humans should be considered a sentinel event and demonstrates that resistance once it occurs may not be

easily reversed and that prevention is a much better strategy that a control strategy.

[Slide shown.]

The next slide shows similar data in the United Kingdom. Again what you can see is introduction in the yellow box of a type of quinolone antibiotic in animals and then the increase shows, the increase in resistance, not just in a number of different animal species but in humans also.

And then finally, the Canadian data, which is really quite dramatic, published this year from Quebec, and what this shows is changes in cephalosporins. This is a common antibiotic that we use, changes in cephalosporin resistance in chicken and human Salmonella and chicken E. coli strains that appear to be related to changes in the use of a type of similar antibiotic in animals, and what you see is a marked decline in those resistance in the E. coli and the Salmonella following a decision for voluntary reduction of the antibiotic in animals, and what is not on this slide is, if you follow out to 2, 3 years, there was a limited reintroduction of that antibiotic for animals, and you see a little spike again as the antibiotic is reintroduced. So very nice, clean evidence of what happens. You introduce the animal. You reduce the antibiotic into the animal population and increase in resistance, and then some examples of a decrease in resistance associated with discontinuing the antibiotic in animals.

Now, studies in Europe have also demonstrated the most compelling and direct links between non-therapeutic use, often referred as subtherapeutic use or use for growth promotion, et cetera, in food-producing animals and subsequent antimicrobial resistance in humans. So the ban of growth promoters in Denmark has prevented spread of vancomycin-resistant enterococcus in humans, reduced resistance in pathogens like Campylobacter and reduced serious human infections, for example, due to specific types of resistant Campylobacter, and this conclusion has been independently verified by the World Health Organization.

Finally, antibiotics are a critical in our Nation's defense against infectious diseases and we need to take strong measures to make sure that we maintain their effectiveness. This subcommittee and my colleagues at HHS and USDA have focused on elements of a comprehensive strategy to protect public health by avoiding resistance that stems from the overuse of antibiotics in animals. Consistent with this one health approach to the prevention of infectious diseases, CDC supports these efforts to minimize non-judicious use of antibiotics in both animals and humans for better human health, animal health and environmental stewardship.

Thank you again for the invitation to testify today and I will be happy to answer any questions.

[The prepared statement of Admiral Khan follows:]

Testimony before the
Subcommittee on Health
Committee on Energy & Commerce
U.S. House of Representatives

Statement of
Ali Khan, MD, MPH
Assistant Surgeon General and Acting Deputy Director,
National Center for Emerging & Zoonotic Infectious Diseases (proposed),
Centers for Disease Control & Prevention,
U.S. Department of Health & Human Services

For Release upon Delivery
Expected at 2:00 p.m.
Wednesday, July 14th, 2010

Good morning Chairman Pallone, Ranking Member Shimkus, and members of the Subcommittee. I am Ali Khan, an Assistant Surgeon General and acting Deputy Director of the National Center for Emerging & Zoonotic Infectious Diseases (proposed), at the Centers for Disease Control & Prevention (CDC). Thank you for the invitation to address the Subcommittee on the available data as it relates to antimicrobial use in food animals. Today I will expand upon the recent testimony before this Subcommittee by CDC Director Dr. Thomas Frieden, and describe: 1) CDC's role in monitoring antimicrobial resistance in humans as it relates to the food supply, 2) data available from North America, 3) data available from Europe, and 4) why appropriate antimicrobial use is critical to protecting human and animal health, as outlined in the Food and Drug Administration's (FDA) recently released draft guidance.

Background

Antimicrobial agents[1] are used to treat infections by different disease-causing microorganisms, including bacteria, mycobacteria, viruses, parasites and fungi. In the vast majority of cases where antimicrobials are used, the microorganisms have found a way to evade or resist the antimicrobial agent.[2] Resistance occurs wherever antimicrobials are used [3]-- in the community, on the farm, and in healthcare settings. Antimicrobial resistance is a global problem, and our most significant global health threats include multi-drug resistant tuberculosis and drug-resistant malaria. Today, however, I will focus on a specific antimicrobial resistance, antibiotic-resistant bacteria as they relate to food animals.

[1] Antimicrobial agents or antimicrobials are general terms for the drugs, chemicals, or other substances that either kill or slow the growth of microbes. Among the antimicrobial agents in use today are antibiotic drugs (which kill bacteria), antiviral agents (which kill viruses), antifungal agents (which kill fungi), and antiparisitic drugs (which kill parasites). An antibiotic is a type of antimicrobial agent made from a mold or a bacterium that kills, or slows the growth of other microbes, specifically bacteria. Examples include penicillin, streptomycin, and other antibiotics discussed below.
[2] Levy, S, Marshall B, Antibacterial resistance worldwide: causes, challenges and responses. NATURE MEDICINE SUPPLEMENT 10:12, 2004.
[3] Tacconelli, Evelina. Antimicrobial use: risk driver of multi-drug resistant microorganisms in healthcare settings.*Current Opinion in Infectious Diseases*. 2009, 22:352-358.

Many of the bacteria in food that cause disease are found in the intestinal tract of animals or people. Healthy food-producing animals commonly carry bacteria that can cause illness in humans, including *Salmonella* and *Campylobacter*.

When an ill person is treated with an antibiotic to which the bacteria is resistant, the antibiotic will not help and may even make the illness worse. In addition, sub-therapeutic use may be more likely to contribute to the development of resistant bacteria. The illness may last longer, be more serious, or more expensive to treat.

In 1989, the Institute of Medicine (IOM) published a report which concluded that the committee could not find direct evidence that subtherapeutic use of penicillin and tetracycline in animal feed was associated with a human health consequence.[4] The committee was unable to distinguish the human health consequence of subtherapuetic use in animals from the widespread therapeutic use of penicillin and tetracycline in humans and animals (primarily due to a lack of data on quantities of antimicrobials used). In 2002, the Alliance for Prudent Use of Antimicrobials (APUA) FAAIR Report (Facts about Antimicrobials in Animals and the Impact on Resistance) concluded that antimicrobial use in animals does contribute to human antimicrobial resistance and results in an adverse human health consequence.[5] The committee concluded: "the elimination of nontherapeutic use of antimicrobials in food animals and in agriculture will lower the burden of antimicrobial resistance in the environment, with consequent benefits to human and animal health."

To protect both human and animal health, appropriate antibiotic use is encouraged for food-producing animals, which is similar to actions associated with use in humans. CDC's activities

[4] Human health risks with the subtherapeutic use of penicillin or tetracyclines in animal feed
Committee on Human Health Risk Assessment of Using Subtherapeutic Antibiotics in Animal Feeds, Institute of Medicine, Division of Health Promotion and Disease Prevention. Published 1989 by National Academy Press in Washington, D.C.
[5] Clinical Infectious Diseases 2002;34:i–I DOI: 10.1086/512410.The Need to Improve Antimicrobial Use in Agriculture Ecological and Human Health Consequences available at http://www.journals.uchicago.edu/toc/cid/2002/34/S3.

related to resistance from antibiotic use in humans have focused on two goals: preventing the emergence and spread of resistant bacteria, and increasing appropriate antibiotic use to reduce the emergence of resistance. In order to minimize the selective pressure of antibiotics, it is important to make sure that when antibiotics are used, they are used appropriately, for either humans or animals. Through population-based surveillance, CDC is able to provide national estimates of disease burden and to track changes in disease burden over time for both resistant community-associated and healthcare-associated bacterial infections. CDC's educational campaign Get Smart: Know When Antibiotics Work has reduced antibiotic use for acute respiratory tract infections among both children and adults.[6] Parallel to antibiotic use in humans, movement toward appropriate antibiotic use for food-producing animals is needed, as discussed in FDA's draft guidance. .

Antimicrobial resistant pathogens can move through the food supply. The use of certain antibiotics in animal feed has been a major driver for some drug-resistant organisms, such as vancomycin-resistant enterococci.[7] There is also evidence of an association between drug use in food animals and the emergence of resistance in some more common enteric pathogens like *Salmonella*.[8] Drug-resistant infections in humans could emerge from exposure to bacteria harbored by animals that are pathogenic to humans, or the genes that cause that resistance could move from bacteria harbored by animals to those bacteria harbored by humans.

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[6] CDC's Get Smart: Know When Antibiotics Work program is a comprehensive public health effort to help reduce the rise of antibiotic resistance. Partnerships with public and private health care providers, pharmacists, a variety of retail outlets, and the media result in broad distribution of the campaign's multi-cultural/multi-lingual health education materials for the public and health care providers. Through Get Smart, CDC develops clinical guidance and principles for appropriate antibiotic use to prevent and control antibiotic resistant upper respiratory infections. Data from the National Ambulatory Medical Care Survey (NAMCS) confirm the campaign's impact on reducing antibiotic use for acute respiratory tract infections among both children and adults. There has been a 20 percent decrease in prescribing for upper respiratory infections (in 1997 the prescription rate for otitis media in children < 5 years of age was 69 prescriptions per 100 children compared to 47.5 per 100 children in 2007) and a 13 percent decrease in prescribing overall for all office visits (overall antibiotic prescribing dropped from 13.8 prescriptions per 100 office visits to 12.0 prescriptions per 100 office visits comparing 1997-98 to 2005-06). The Get Smart: Know When Antibiotics Work campaign contributed to surpassing the Healthy People 2010 target goal to reduce the number of antibiotics prescribed for ear infections in children under age 5.

[7] Bonten et al., Lancet 2001. Endtz et al., J Clin Microbiol 1997. Klare et al., Microb Drug Res 1999. Schouten et al.. Lancet 1997.

[8] Dutil et al., Emerg Infect Dis 2010. Angulo et al,, J Vet Med 2004. Spika et al, NEJM 1987. Holmberg et al., NEJM 1984.

NARMS

The National Antimicrobial Resistance Monitoring System (NARMS) for Enteric Bacteria was established in 1996 for the purpose of 1) monitoring trends in the prevalence of antibiotic resistance among bacteria isolated from humans, retail meats (began 2002), and food animals; 2) disseminating public health information on antibiotic resistance; 3) promoting interventions that reduce resistance among enteric bacteria; and 4) informing the approval process for the use of antibiotic agents in veterinary medicine. NARMS is a collaboration among CDC (human samples), the Food and Drug Administration's (FDA) Center for Veterinary Medicine (retail meats), and the United States Department of Agriculture's (USDA) Agricultural Research Services (animal samples).

CDC's Role in NARMS

For the human component of NARMS, participating health departments forward every twentieth non-Typhi *Salmonella* isolate, every *Salmonella* Typhi, every twentieth *Shigella* isolate, and every twentieth *E. coli* O157 isolate received at their public health laboratories to CDC for antibiotic susceptibility testing.[9] Sites participating in FoodNet, the Foodborne Diseases Active Surveillance Network, also submit a representative sample of *Campylobacter* isolates from humans to CDC for susceptibility testing.[10] In addition, NARMS participates in outbreak investigations involving these bacteria and conducts further studies on resistance mechanisms.

[9]Antimicrobial susceptibility testing currently involves the determination of the minimum inhibitory concentration (MIC) for 17 antimicrobial agents: amikacin, ampicillin, amoxicillin-clavulanic acid, apramycin, cefoxitin, ceftiofur, ceftriaxone, cephalothin, chloramphenicol, ciprofloxacin, gentamicin, imipenem, kanamycin, nalidixic acid, streptomycin, sulfamethoxazole, tetracycline, and trimethoprim-sulfamethoxazole.

[10] FoodNet sites submit all Campylobacter isolates (Georgia, Maryland, New Mexico, Oregon, Tennessee), every other isolate (California, Colorado, Connecticut, New York), or every fifth isolate (Minnesota) to NARMS based on the burden of campylobacteriosis in each site. Susceptibility testing of Campylobacter is performed to determine the MICs for nine antimicrobial agents: azithromycin, ciprofloxacin, clindamycin, erythromycin, florfenicol, gentamicin, nalidixic acid, telithromycin, and tetracycline.

NARMS data for human isolates have been collected continually since 1996, which makes trend analysis possible; the data provide information about patterns of emerging resistance, which in turn guide mitigation efforts. Because antibiotic use in food-producing animals may result in antibiotic resistance among bacteria that can be transmitted to humans through the food supply, antimicrobial resistance data from humans are important for the development of public health regulatory policy for the use of drugs in food-producing animals.

In addition to NARMS, CDC has developed a prudent use educational program called "Get Smart: Know When Antibiotics Work on the Farm" to promote appropriate antibiotic use in food producing farm animals. CDC funds and provides technical assistance for several state-based efforts to educate veterinarians and food producers including those in the dairy and beef industries. Educational modules have been developed for use in veterinary professional curricula, which are case-based and are tailored for given animal species and/or food animal production type.

North American Data

Non-typhoidal *Salmonella* causes approximately 1.4 million cases of disease in humans in the United States each year. Patients with complicated or severe infections are treated with fluoroquinolones or cephalosporins, and of these two drug classes, only cephalosporins are approved for treatment of children with these infections. Since NARMS began surveillance in 1996, cephalosporin resistance among *Salmonella* isolated from humans has increased significantly, and a similar resistance also has been found among *Salmonella* isolated from livestock and retail meats. In many cases, the same types of bacteria and genetic mechanisms of resistance are found in both human and animal sources.

For example, studies related to *Salmonella* as both a human and animal pathogen, including many studies in the United States, have demonstrated that (1) use of antibiotic agents in food

animals results in antibiotic resistant bacteria in food animals, (2) resistant bacteria are present in the food supply and are transmitted to humans, and (3) resistant bacterial infections result in adverse human health consequences (e.g., increased hospitalization[11]). The following examples demonstrate the movement of resistant pathogens through the food supply, and exacerbate our concern about the link between the use of antibiotics in animals and eventual human health effects:

- Multi-drug resistant (MDR) *Salmonella* Newport has emerged, which has caused numerous outbreaks where the source was ground beef. Ground beef samples have been found with the same molecular fingerprint as the human strain.[12]
- As described in scientific articles published this year, Cephalosporin-resistant *Salmonella* Heidelberg has emerged among humans, and molecular fingerprinting indicates that strains responsible for human infections are indistinguishable from cephalosporin-resistant *Salmonella* Heidelberg isolated from retail poultry sources.[13] These findings support work done by the Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS) that demonstrated a strong correlation between cephalosporin-resistant *Salmonella* Heidelberg isolated from retail chicken and the incidence of cephalosporin-resistant *Salmonella* Heidelberg infections in humans across Canada. CIPARS also published this year that in Quebec, changes in cephalosporin-resistance in chicken and human *Salmonella* Heidelberg and chicken *E. coli* strains appeared to be related to changes in ceftiofur use in poultry hatcheries.[14]

[11] Varma *et al.*, J Infect Dis 2005.
[12] Gupta et al., J Infect Dis 2003. CDC MMWR Morb Mortal Wkly Rep 2002.
[13] Folster et al., Foodborne Pathog Dis 2010 and Zhao et al., Appl Environ Microbiol 2008.
[14] Dutil et al., Emerg Infect Dis 2010

Studies of another bacterium, *Campylobacter*, also demonstrate movement of resistant pathogens through the food supply. *Campylobacter* is one of the leading causes of culture-confirmed foodborne bacterial disease in humans in the United States, and consumption of poultry has been shown to be an important risk factor for *Campylobacter* infection. Fluoroquinolones and macrolides are the drug classes of choice for treating *Campylobacter* infections. Following the approval of fluoroquinolones for use in poultry, resistance to this class of drugs among human *Campylobacter* isolates rose sharply, to more than 20%.[15] FDA has since withdrawn approval of fluoroquinolones for use in poultry, and NARMS continues to monitor *Campylobacter* from humans, retail meats and food animals for fluoroquinolone resistance.

Persistence of fluoroquinolone-resistant *Campylobacter* in domestic food animal and retail meat sources suggests that these strains may be able to compete well with susceptible strains in food animal environments, even in the absence of antimicrobial selective pressure.[16] Additional studies are underway to better understand the contribution of foreign travel to fluoroquinolone-resistant campylobacteriosis and estimate the burden of illness associated with domestically-acquired infections.

The Danish Experience

Multiple studies about the Danish experience have demonstrated the link between non-therapeutic use of antimicrobial agents in food-producing animals, particularly swine and broiler

[15] Multiple NARMS related publications available at http://www.cdc.gov/search.do?subset=enterics&q=pathogencampylobacter&filter=p

[16] Zhang Q, Lin J, Pereira S. (2003) Fluoroquinolone-resistant *Campylobacter* in animal reservoirs: dynamics of development, resistance mechanisms and ecological fitness. *Anim Health Res Rev* 4:63–71

chickens, and antimicrobial resistance found in animals and humans.[17,18,19,20,21,22] Non-therapeutic uses include promoting growth and improving feed efficiency; drugs for these purposes are typically given in animal feed.

In 1995, the Danish government banned the non-therapeutic use of avoparcin for growth promotion in Denmark; the European Union (EU) adopted the same ban in 1997. In 1998, Denmark banned use of virginiamycin for growth promotion. Subsequently, the Danish cattle and broiler industries voluntarily stopped the non-therapeutic use of all antibiotics for growth promotion in 1998, while the Danish swine industry through voluntary and regulatory action stopped all non-therapeutic use of antibiotics for growth promotion in swine above 35 kg by February 1998 and for all age groups by December 1999. The EU phased in bans for certain drugs in 1999, and then voted to phase out all non-therapeutic use of antibiotics for growth promotion in 2002, which began 2006.

Since the stoppage of non-therapeutic use in Denmark, therapeutic use in swine has increased. However, total antimicrobial consumption in swine has decreased from 100 to 49 milligrams of antimicrobials per kilogram of meat produced, a 50% reduction. In addition, stopping the use of various non-therapeutic antibiotic growth promoters (e.g., avilamycin, avoparcin, spiramycin,

[17] World Health Organization. 2003. Impacts of antimicrobial growth promoter termination in Denmark: The WHO international review panel's evaluation of the termination of the use of antimicrobial growth promoters in Denmark.Available at: http://www.who.int/salmsurv/en/Expertsreportgrowthpromoterdenmark.pdf.

[18] DANMAP. 2008. *Use of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from food animals; foods and humans in Denmark*. Available at: http://www.danmap.org/pdfFiles/Danmap_2008.pdf.

[19] Aarestrup, F.M., A.M. Seyfarth, H.D. Emborg, K. Pedersen, R.S. Hendriksen, and F. Bager. July 2001. "Effect of Abolishment of the Use of Antimicrobial Agents for Growth Promotion on Occurrence of Antimicrobial Resistance in Fecal Enterococci from Food Animals in Denmark," *Antimicrobial Agents and Chemotherapy* 45(7): 2054-2059. Available at: http://aac.asm.org/cgi/reprint/45/7/2054.

[20] Boerlin, P., A. Wissing, F. M. Aarestrup, J. Frey, and J. Nicolet. 2001. "Antimicrobial Growth Promoter Ban and Resistance to Macrolides and Vancomycin in Enterococci from Pigs," *Journal of Clinical Microbiology* 39(11): 4193--4195. Available at: http://jcm.asm.org/cgi/reprint/39/11/4193.

[21] Evans, M.C. and H.C. Wegener. 2003. "Antimicrobial Growth Promoters and Salmonella spp., Campylobacter spp. In Poultry and Swine, Denmark," Emerging Infectious Diseases 9(4): 489-492. Available at: http://www.cdc.gov/ncidod/eid/vol9no4/pdfs/02-0325.pdf

[22] Gravea, K., V.F. Jensen, K. Odensvik, M. Wierup, and M. Bangen. 2006. "Usage of veterinary therapeutic antimicrobials in Denmark, Norway and Sweden following termination of antimicrobial growth promoter use," Preventive Veterinary Medicine 75(1-2): 123-132.

tylosin, virginiamycin) has resulted in a major reduction in antimicrobial resistance as measured among several different bacterial species in food animals and food. Furthermore, resistance to these drugs among *Enterococcus* isolated from broilers, swine, and the meat from these animals decreased. In 2003, the World Health Organization (WHO) could not determine the ban's direct and total effect on antimicrobial resistance in humans because of limited data.[23] However, more recent susceptibility data from enterococci isolated from healthy persons in the community show a decline in resistance of enterococci isolated from healthy people in the community in Denmark following the ban on antimicrobial growth promoters. [24]

Production and economic impacts from the ban are described in a 2003 WHO report. Mortality among weaning age pigs increased several years before as well as a few years after non-therapeutic use stopped, but has drastically decreased in recent years, indicating that the termination had no effect on swine mortality. In addition, the WHO reports that: "Overall, total volume of pork production in Denmark continued to increase in the period following the termination of antimicrobial growth promoters... The net costs associated with productivity losses incurred by removing antimicrobial growth promoters from pig and poultry production were estimated at 7.75 DKK (1.04 €) per pig produced and no net cost for poultry. This translates into an increase in pig production costs of just over 1%."[25]

In summary, non-therapeutic use has been shown to lead to an increase in resistant strains in animals in Denmark. The Danish experience demonstrates that it is possible to stop these uses, reduce overall use of antibiotics in animals, reduce resistant circulating bacteria that can

[23] World Health Organization. 2003. Impacts of antimicrobial growth promoter termination in Denmark: The WHO international review panel's evaluation of the termination of the use of antimicrobial growth promoters in Denmark. Available at: http://www.who.int/salmsurv/en/Expertsreportgrowthpromoterdenmark.pdf.
[24] Annual reports of the Danish Integrated Antimicrobial Resistance Monitoring and Research Programme (DANMAP) available at www.danmap.org
[25] World Health Organization. 2003. Impacts of antimicrobial growth promoter termination in Denmark: The WHO international review panel's evaluation of the termination of the use of antimicrobial growth promoters in Denmark.Available at: http://www.who.int/salmsurv/en/Expertsreportgrowthpromoterdenmark.pdf.

infect humans, and not have industry or consumers significantly affected by decreased production or increased costs.

Conclusion

Antibiotics are a critical asset in our nation's defense against infectious disease, and we need to take strong measures to ensure that we maintain their effectiveness. Since antimicrobial agents were first used widely in the last century, almost every type of clinically relevant bacteria has developed antibiotic resistance. This Subcommittee, and my colleagues at HHS, have rightly focused on elements of a comprehensive strategy –avoiding resistance that stems from over-use in both humans and animals, and developing new antibiotics. CDC continues to take steps to minimize inappropriate use of antibiotics in humans, and today's hearing is an important opportunity to highlight the need for parallel steps to minimize inappropriate antibiotic use in animals.

As a nation, we must do more to respond to this growing problem. CDC supports FDA's approach, as described in recent guidance, that the use of antimicrobials should be limited to protecting human and animal health. Purposes other than the protection of animal or human health should not be considered judicious use.

Thank you again for the invitation to testify before you today. I will be happy to answer any questions you may have.

Mr. PALLONE. Thank you very much. I thank all of you.

We have three votes, the last votes of the day, about half an hour or so, and so we are going to stand in recess.

Mr. SHIMKUS. Mr. Chairman, will you yield for a minute? During the break, could we ask the majority since those slides weren't provided as far as I know in the testimony, that we get copies of those slides?

Mr. PALLONE. Yes, we will get copies for you.

Mr. SHIMKUS. Thank you.

Mr. PALLONE. So we will stand in recess.

Mr. WAXMAN. Mr. Chairman, before we break, may we renew our unanimous consent request to put the——

Mr. PALLONE. I am sorry, Mr. Chairman.

Mr. WAXMAN. Oh, we did it already?

Mr. PALLONE. They have all been entered including Ms. Schakowsky's. They have all been entered.

Mr. SHIMKUS. I was all over it for you.

Mr. PALLONE. The subcommittee stands in recess.

[Recess.]

Mr. PALLONE. The subcommittee hearing will reconvene. We are going to have questions now, and I will start with myself for 5 minutes.

This is sort of—I am going to cover all three of you with this. I will start with Dr. Sharfstein.

At the end of last month, as you mentioned, the FDA released a draft guidance on the judicious use of medically important antimicrobial drugs in food-producing animals, and as I understand it, the guidance essentially says that antibiotics that are important for treating human disease should not be used in animals except as needed to assure their health, and it also says that veterinarians should be involved when the antibiotics are used for that purpose. So I guess my point is to note that today medically important antibiotics, whether important for treating people or treating animals, are used for non-therapeutic purposes, and so many of the people who use them for those purposes, Dr. Sharfstein, haven't necessarily reacted to your guidance in a positive way.

So my questions are about the scientific basis for the guidance. What led you to develop the guidance? Did you meet with stakeholders such as industry that would be affected by the policies? What has been the general reaction to the guidance? Who supported it? Who has opposed it? I mean, we know that the producers aren't happy about it. On the day your guidance was released, the president of the National Pork Producers Council said FDA didn't present any science on which to base this. So that is my question, really, is it scientifically based? What is your response to the naysayers?

Dr. SHARFSTEIN. Well, we look forward to the comment period and we will review everything that we get from different groups officially. I actually have been impressed at the interest across many different areas of the animal agriculture in working with FDA and I will note that the Animal Health Institute, that they welcome the guidance, and the AVMA said that they were pleased that we are committed to working with the veterinary profession to address antimicrobial resistance concerns.

So I think it may be—you know, I wouldn't necessarily buy into us versus them on this. I think that is a very sensible path. It really rests on a mountain of strong science, and one of the documents we cite, I think is really excellent. It is the WHO 2003 report which walks through six lines of evidence that exists, citing multiple studies including a number done in the United States, and the six are outbreak investigations which trace Salmonella infections to farms, epidemiological investigations which demonstrate that people are more likely to have visited or lived on a farm prior to illness, that they have antimicrobial-resistant infections, field studies including some I think you will hear about on the next panel where they actually prospectively demonstrate how antimicrobial use in food animals selects for the emergence of resistance, case reports including children who have been sick, spatial and temporal associations where countries where they use less antimicrobial agents you see less antimicrobial resistance in bacteria, and finally, molecular subtyping, so this is the sixth type of evidence, and I will be happy to submit this to the record—it is cited in our report—where you actually can trace the specific bacteria around, and they find—and one of the studies I found most interesting, I think it was from Minnesota, is that the resistant strains of the bugs in humans match the resistant strains in the animals and those match the sensitive strains in the animals except for the resistance genes, but the sensitive strains in humans don't match those. So you think it basically looks like the resistance is coming from the animals and the animal resistance is developing in the animals, and they do that by molecular analysis of the actual bacteria.

So I really do think there is a very strong foundation of evidence. I think Dr. Khan——

Mr. PALLONE. Well, let me ask the other two guys.

Dr. Khan, do you agree with Dr. Sharfstein on this, and Dr. Clifford, do you believe that growth promotion is an injudicious use of antibiotics? Basically if you would comment.

Admiral KHAN. CDC supports the FDA position. The position is consistent with the one health approach and essentially how we use antibiotics for human use, and a number of members of the committee have pointed that tout. So we use antibiotics in humans specifically for treatment, for prophylaxis when it is a specific targeted individual or targeted drug for targeted indication, and those are the three uses in antibiotics. So, you know, I have kids in daycare, and lots of them are infected with all sorts of things. Nobody would ever propose that all children in daycare, for example, should be on antibiotics through that whole time frame. So this is very consistent with the one health approach and how we deal with antibiotics in humans.

Mr. PALLONE. Dr. Clifford?

Dr. CLIFFORD. We work very closely with FDA in consultation with this document and provided feedback to them. We think this is a good first step, and we welcome seeing the comments as well that FDA receives on this particular document.

As far as whether growth promotion or judicious use of antibiotics, our position is that with regards to judicious use of medically important antibiotics, we are talking about treatment, control and prevention of animal health issues and disease. So there are

antibiotics, though, that are used, or antimicrobials that are used in animals that have no analog being used in human medicine and should not be of concern unless there is proven evidence to the human side.

Mr. PALLONE. OK. Thank you all.

Mr. Shimkus.

Mr. SHIMKUS. Thank you, Mr. Chairman.

Dr. Clifford, is there science to support the removal of antibiotic use for growth promotion?

Dr. CLIFFORD. I am sorry?

Mr. SHIMKUS. Is there science to support the removal of antibiotic use for growth promotion?

Dr. CLIFFORD. You mean as far as the cause and effect?

Mr. SHIMKUS. Right.

Dr. CLIFFORD. There is some cases.

Mr. SHIMKUS. Well, can you cite them?

Dr. CLIFFORD. Well, obviously you can cite the Danish experience.

Mr. SHIMKUS. No, I am talking about United States.

Dr. CLIFFORD. Not right offhand, no, I cannot.

Mr. SHIMKUS. Do you know of any U.S.-supported research peer review?

Dr. CLIFFORD. I cannot cite any.

Mr. SHIMKUS. You are similar to other testimony we received in April where Dr. Fauci and also quoted Dr. Frieden, and this is the hearing record. "To my knowledge and to Dr. Frieden's knowledge, I don't think any of those studies have been done in the United States."

I mean, I saw Dr. Sharfstein give you a note. The question is for you, not for Dr. Sharfstein. Dr. Sharfstein, I will ask you questions if you have—with my time available.

Equating animals to people is like equating an apple to an orange. I am just—that is why we have vets and that is why we have doctors. That is why vets are not qualified to work on human beings or medical doctors qualified for animals unless I am sure in parts of southern Illinois years ago but—let me ask Dr. Sharfstein. What decreases in the level of human antibiotic resistance will we see if FDA proceeds with this Guidance 209 document as currently proposed?

Dr. SHARFSTEIN. I expect that if we go forward with Guidance 209 as currently proposed that this will reduce antibiotic resistance pressure. We will have less antibiotic resistance in animals and less antibiotic resistance in humans, and it will promote both human and animal health.

Mr. SHIMKUS. And by what percent?

Dr. SHARFSTEIN. I don't think I can answer the exact percentage.

Mr. SHIMKUS. And can you cite me a study, a U.S. study that verifies that analysis and that answer?

Dr. SHARFSTEIN. Yes, I can. The Institute of Medicine's 2003 report was very clear that this would be the right approach to take for this reason.

Mr. SHIMKUS. Is that a study and is it peer-reviewed science?

Dr. SHARFSTEIN. It is a study, and they do have a peer-review process at the Institute of Medicine. The Institute of Medicine is

considered our Nation's leading scientific expert, you know, group. They looked at this issue. They said to do nothing is in effect to allow the continued evolution of antimicrobial-resistant microbes which poses serious and long-term——

Mr. SHIMKUS. And let me—and what do we see as a national government? Have we done any additional research to verify their findings?

Dr. SHARFSTEIN. There has also been research in King County related to Campylobacter that is very compelling. There is a New England Journal study from Minnesota that is very compelling. I would be happy to submit all these studies for the record.

Mr. SHIMKUS. We would like them all, please.

Dr. SHARFSTEIN. Dr. Frieden mentioned in his letter to the committee that there is extensive data from the United States.

Mr. SHIMKUS. Yes, correcting the record by which he was quoted in April, and we find that curious and also timely that that occurred.

Dr. Khan, I want to go to your slides that you had presented to us, and if the staff could pull up slide number 1 for me from Dr. Khan's. I am sorry. We should have given you a heads-up, but if we didn't, we apologize. That is the right one.

The antibiotics on chart 1 are mostly used for therapeutic use, not subtherapeutic use. Is that correct?

Admiral KHAN. Yes.

Mr. SHIMKUS. I see that there was no reduction in the little arrow there for those who have it. That is when it has been removed. There was no—in fact, there is an increase after it was removed. What does that say?

Admiral KHAN. That says prevention is really a lot more important than control, so these may represent sentinel events. The moment you get a resistant bacteria from animals that makes it way into the human population, there is a different set of drivers for maintaining it in humans that makes it impossible to shut it down.

Mr. SHIMKUS. Could it be that there is another cause for the resistance other than for which we are speaking of today?

Admiral KHAN. I think the data is pretty unequivocal. Before the use of fluoroquinolone——

Mr. SHIMKUS. Well, let us go to the second slide. Let us talk about this unequivocal data here. This is the, I can't pronounce it, quinolone resistance, Salmonella and typhimurium. First question. I was elected to Congress in November of 1996, took office in 1997. This chart ends in 1997, 14 years ago. Is there no data after that?

Admiral KHAN. There is data after that.

Mr. SHIMKUS. And what does that data show?

Admiral KHAN. The data shows continued resistance. The purpose of this specific slide was to show that the introduction of this antibiotic into animals led to an increase in resistant bacteria in not just——

Mr. SHIMKUS. I think if you would add data, I think what we can find, and maybe this is why it was not submitted is that you are going to see a decrease, and if that is the case, I find it very perplexing and very troubling that we use data from 1997 and we don't go to 14 years later to show the path.

Mr. Chairman, I know my time is expired, but the last thing, I also have problems with the third slide. That is the importance of getting data and information here in a timely manner so we can check sources, and to use World Health Organization data, to have dumbed down from the Danish study which will make the Danish products competitive because it is going to make us more difficult to compete. We are dumbing down our ability, is very problematic and I would agree with some of my colleagues, even on the other side, we better go very, very carefully and use real science in this antibiotics use of animals, and I yield back my time.

Mr. PALLONE. Chairman Waxman.

Mr. WAXMAN. Dr. Khan, just on that last question you were asked, if you had more data, you say it would show the same results as what you saw in 1997?

Admiral KHAN. It depends on the country, sir. So in the U.K. there is continued persistence. In the United States, using National Antibiotic Resistance Monitoring System, NARMS, which is a system we use with FDA, that FDA, USDA and CDC sponsors, there is variable data for different pathogens that shows either continued increase or for some select Salmonellas decreases in resistance. The reason I used—so the first slide is actually U.S. data, fluoroquinolones in the United States, unequivocal that the moment you use the fluoroquinolones, within 2 to 3 years from less than 1 percent you went up to 20 percent resistance. That has remained——

Mr. SHIMKUS. Mr. Chairman, I don't want to be disrespectful, but the point is, that is for therapeutic——

Mr. WAXMAN. Just a minute. You are disrespectful.

Mr. PALLONE. Chairman Waxman has the time.

Mr. SHIMKUS. Well, I was hoping you yield, but I apologize.

Mr. PALLONE. No, he is not yielding at this time.

Mr. WAXMAN. Go ahead. He doesn't like the answer you are giving but let us hear what it is.

Admiral KHAN. So that initial data, sir, the fluoroquinolone data is U.S. data. We also have abundant additional U.S. studies showing this. So if we look at Salmonella typhimurium DT–104, multi-resistant outbreak amongst people, that was due to ground beef. If we look at Salmonella Newport, this is a multi-resistant strain——

Mr. WAXMAN. Well, let me ask you this because in USA Today on Monday, the director of the National Pork Producers Council said that, "According to top scientists with the Centers for Disease Control and Prevention and the National Institutes of Health, there are no scientific studies linking antibiotic use in livestock production with antibiotic resistance in people." Is this an accurate reflection of CDC's views?

Admiral KHAN. Sir, Director Frieden has submitted a letter to the committee that specifically states that there is a compelling body of evidence to demonstrate this link that is summarized above, so there is multiple North American studies that describe how use of antibiotics in animals results in resistant bacteria in food animals. These resistant bacteria then are present in the food supply and transmitted to humans. And finally, these resistant bacteria can result in adverse human health consequences such as

increased hospitalization, and there is good scientific evidence for each one of those three assertions.

Mr. WAXMAN. Well, a large part of the confusion seemed to stem from the question about the adequacy of the peer-reviewed literature showing a link between antibiotics use in animals and resistant infections in humans. Do you think there is substantial scientific evidence demonstrating a link between antibiotic use in animals and infections in humans, and can you discuss the implications of European versus USA data?

Admiral KHAN. So there is an unequivocal evidence and relationship between use of antibiotics in animals and transmission of antibiotic-resistant bacteria causing adverse effects in humans following that pathway that I have outlined. The Danish data is also very clear on the use of subtherapeutic use of antibiotics for animals and what the consequences on resistance in humans.

Mr. WAXMAN. Dr. Sharfstein, do you think there is substantial scientific evidence demonstrating a link between antibiotic use in animals and infections in humans?

Dr. SHARFSTEIN. Yes, I do think that.

Mr. WAXMAN. And is this scientifically controversial?

Dr. SHARFSTEIN. I don't believe so, no.

Mr. WAXMAN. I wanted to ask a different line of questions, and that is regarding, as we consider antibiotic use in animals, we have heard concerns from some of the producers that reducing the routine use of antibiotics in animals could result in increased risk of foodborne illnesses. Since we have representatives of two of the country's leading public health agencies, I would like to ask you about your assessment of the risks and benefits of reducing the use of antibiotic use in animals. I think it is important to understand that no one here is proposing to ban the use of antibiotics for animals. The goal here is to reduce the use of antibiotics that are important to human health and animals, particularly when that use provides little or no benefit to those animals.

Dr. Sharfstein, as you know, it is the mandate of the Food and Drug Administration to ensure that the food supply is as safe as it can be, so would you be concerned if you believed that reducing the use of important human antibiotics in animals could result in increased risk to the food supply?

Dr. SHARFSTEIN. Let me make sure I understand your question. Am I concerned or would it be concerned?

Mr. WAXMAN. Are you concerned if you reduce the use of antibiotics in animals that affect humans that this could result in increased risk to the food supply?

Dr. SHARFSTEIN. I think with our guidance, we are talking about the use for not-health purposes, so we don't believe if we are eliminating the use for not-health purposes we are going to have adverse health consequences.

Mr. WAXMAN. Is there evidence to support the claim that phasing out certain uses of antibiotics could increase risks to the food supply?

Dr. SHARFSTEIN. I think if by certain uses you mean the uses we are proposing phasing out, you know, for growth promotion, feed efficiency, I would say no, there is not evidence.

Mr. WAXMAN. Dr. Khan, you are the Nation's leading epidemiologist at CDC as well as the agency tasked with conducting outbreak investigations foodborne illness. Would CDC be concerned if it believed that phasing out certain use of antibiotics in animals would increase the risk of illness in humans?

Admiral KHAN. No, sir, there is no scientific evidence suggesting a negative impact on human health for limiting the non-judicious use of antibiotics in animals.

Mr. WAXMAN. Thank you.

Thank you, Mr. Chairman.

Mr. PALLONE. Thank you.

Next is the gentleman from Indiana, who has 8 minutes. Mr. Buyer.

Mr. BUYER. Thank you very much.

Dr. Clifford, I have a question that deals with adulterated, counterfeit, knockoff drugs. We have a problem in our country, and countries around the world are challenged by this. Do you see any escalation or any evidence of adulterated counterfeit drugs in animal health?

Dr. CLIFFORD. Congressman, since this really falls under FDA's jurisdiction, I would have to turn to them to answer that question.

Dr. SHARFSTEIN. In the United States——

Mr. BUYER. Hold on a second.

Dr. SHARFSTEIN. Oh, I am sorry.

Mr. BUYER. Hold on. Go ahead. Thanks. For animal health.

Dr. SHARFSTEIN. For animal health, I think we are going to have to get back to you. I am not prepared to answer that. I have not heard of a significant counterfeit problem in the United States but I want to make sure and get back to you.

Mr. BUYER. You know, as our problem is growing, it is only time before it migrates. It is going to follow the money, right? Bad guys follow the money. And that is why I asked the question.

I want to thank the FDA for continuing the blitzes that you are doing at international mail facilities, so thank you for doing that. You are trying to "get the word out" to Americans that if you go on the Internet and you think that that is an approved Web site to order your pharmaceutical products, that you are really playing Russian roulette with your life, and so thank you for keeping these blitzes going and trying to get the word out. I noted in your testimony when you were with us in March, you had in your testimony, "Protecting Americans from unsafe or contaminated drugs is not just an important responsibility of the FDA, it is our core charge." Do you agree with that today?

Dr. SHARFSTEIN. I do believe that. I think it is one of the reasons that FDA——

Mr. BUYER. So——

Dr. SHARFSTEIN [continuing]. Was established.

Mr. BUYER. I am sorry?

Dr. SHARFSTEIN. I was saying, it is one of the reasons FDA was established.

Mr. BUYER. You also then in your testimony talked about FDA must adopt a new approach. Now, I think when you talked about your new approach, also you were concerned about the production, i.e., raw ingredients, that are used within our supply chain for

which people are buying at retail outlets within the gold standard of our own country. So ensuring that we maintain that gold standard, you are putting your eyes on that supply chain and production. I don't have any problems with that. I think that is wonderful. I think the Administration is doing what it is supposed to do. I applaud you with regard to your striking the agreements with other countries, putting more inspections on other soils. That is awesome.

With regard to your—it is twofold. Not only do you have that to do but we also have the mail facilities. Now, as we are doing this, we have got both of these going on at the same time, is we are trying to then do our electronic pedigree, and Mr. Dingell has a bill, and we are going to do work and do this electronic pedigree, but let me tell you what I was bothered about what I read in the Miami Dade about your last blitz. I think it is great. Like I said, you are doing the blitz. You did a 3-day blitz. You did everything you were supposed to do, your coordination with Customs, Border Protection, thousands of pieces of foreign mail. You X-rayed them. You separated them. You identified them, the suspicious pharmaceutical products. You ID'd them. You showed how many of them were counterfeit and knocked off, and then you sent them back. America has to be shocked, and the counterfeiters have to be excited that America is a place where you can counterfeit your drugs, send them to America, steal people's money, and the American government will send the counterfeit drugs back to you so you can then send them to someone else that you can steal more money from. This is like one of the dumbest policies I think we have in this country.

Now, last year I sent questions on this, and the answer from FDA is that FDA currently has authority to seek through the judicial process the destruction of any drug and other FDA-related products that relates to the Federal Food, Drug and Cosmetic Act. Now, the person right next to your inspectors, Customs, I mean, there is no wall. You have been there, right? There is no wall between these guys. That customs person, when they see it identified prima facie as knockoff, they destroy it. But if they hand off and give to the FDA person, the FDA says we can't destroy it, put a label on it and they send it back. I know you have got to be uncomfortable with that as a policy. Are you?

Dr. SHARFSTEIN. Yes. I mean, I have spoken to some of the inspectors who are, you know, as frustrated as you are.

Mr. BUYER. All right. Now, if you are willing to step into a new—and that was your testimony that you gave to us in March, that you embrace and wanted to adopt a new approach with regard to the raw ingredients, through production and distribution always to U.S. consumers, I think I have an opportunity. I think, Mr. Dingell, we have an opportunity to help protect America, and that is embrace what the FDA is saying here, Mr. Dingell, and let us figure out how we can destroy these when they are identified, when your inspectors identify them. Let us not send them back to the counterfeiters so they can continue to rip off people. You know, Doc, come on, they are preying upon the most vulnerable of our population, which is awful. Would you be willing to work with Mr. Dingell and

I to come up with a policy here that can give your inspectors the ability to destroy these counterfeit, knockoff, adulterated drugs?

Dr. SHARFSTEIN. Yes, and I believe we have been already starting that process by working with your staff and Congressman Dingell's staff on this issue.

Mr. BUYER. All right. Well, I want to be as proactive as we possibly can. John Dingell, to his credit, started this a long time ago with his paper pedigree, and he has always had a great interest. It goes all the way back many years into the 1970s, and I applaud what he has done. I think he has got to be pretty shocked on where America is today compared to where we were in the 1970s, and as a policy and I know you adopted this, I was just as frustrated with the last Administration but I am embracing your spirit, and if we are able to move ahead, Mr. Dingell, I want to join with you today and I want to work with the FDA and I want to resolve this matter.

I want to yield to the chairman for a second.

Mr. DINGELL. I thank the gentleman. He is most kind to me, and I want to thank him for the kind comments he has made about me. I want to assure him that my assurances of the last Congress, I would be happy to work with him, and I happen to agree with the gentleman about the problem of imports, about tracing pharmaceuticals and other drugs, and I am pleased to report to the gentleman that very shortly we will be circulating a draft for comments about pharmaceutical safety, and I hope that the gentleman when that occurrence happens that he will look at it with sympathy and I look forward to working with him because he is a valuable member of the committee, and I thank him.

Mr. BUYER. I thank the gentleman.

The last, can I do this piece of math? Thirteen——

Mr. PALLONE. The gentleman's time has expired, but all the love——

Mr. BUYER. I ask unanimous consent for 30 seconds.

Mr. PALLONE. Yes, with all the love and bipartisan here——

Mr. BUYER. God bless you.

Mr. PALLONE. I certainly don't want to stop the gentleman.

Mr. BUYER. Thirteen international mail facilities, on average 35,000 are pharmaceutical packages, times 365 days, that is 1,666,075 packages a year. If 80 percent are counterfeit, adulterated or knocked off, that means there are 132,860 pharmaceutical packages that are coming into the country that are either adulterated, counterfeit or knockoff, and people are taking these and they are not metabolizing in the body in ways in which as doctors you intend.

With that, I yield back. Thank you.

Mr. PALLONE. Thank you.

The gentlewoman from—I am sorry. Chairman Dingell is next.

Mr. DINGELL. I thank you, Mr. Chairman.

These questions are for all three witnesses. The first is yes or no. Is there a definitive link between antimicrobial use in animal feed and antibiotic resistance in humans? Starting with Dr. Sharfstein.

Dr. SHARFSTEIN. Yes.

Mr. DINGELL. Our next witness, Doctor.

Dr. CLIFFORD. Yes, some.

Mr. DINGELL. Some?

And you, Dr. Khan.

Admiral KHAN. Yes, sir.

Mr. DINGELL. Now, Dr. Sharfstein, please tell us what scientific studies support your claim.

Dr. SHARFSTEIN. I think the best document that begins to summarize those is this 2003 study from the World Health Organization and it goes through outbreak investigations, epidemiological investigations, field studies, case reports, spatial and temporal associations and molecular subtyping. In each of those areas of research there are studies that support that statement.

Mr. DINGELL. Now, Doctor, if you would like, I would be pleased to have you make other submissions supporting the statement which you just made.

So next question to all three of our panel members. Are these studies based—rather is to Dr. Sharfstein. Are these studies based entirely on the European experience or do we have some that reflect experience in the United States?

Dr. SHARFSTEIN. They are both based on European experience and some that are in the United States including one by someone I went to medical school with.

Mr. DINGELL. Now, again, Dr. Sharfstein, it is my understanding that FDA currently has authority to withhold approval for certain animal drugs if they are use poses a risk to the public health. Is that correct?

Dr. SHARFSTEIN. That is correct.

Mr. DINGELL. OK. Now, does the likelihood that an antimicrobial drug used to treat a food-producing animal may cause antibiotic resistance to a problem in humans to pose a risk, and I put the risk to public health in quotes. What is the answer to that? Do you want me to repeat the question?

Dr. SHARFSTEIN. Yes.

Mr. DINGELL. Does the likelihood that an antimicrobial drug used to treat a food-producing animal may cause an antibiotic resistance problem in humans pose a "risk to public health"?

Dr. SHARFSTEIN. I think that the likelihood that that would happen does factor into the regulatory process as we approve new antimicrobials, so yes.

Mr. DINGELL. And our other two witnesses, Dr. Clifford and Dr. Khan, what is you view on that question?

Dr. CLIFFORD. Could you repeat that question again, please?

Mr. DINGELL. It is a difficult question. All right. Does the likelihood that an antimicrobial drug used to treat a food-producing animal may cause an antibiotic resistance problem in humans pose a "risk to the public health"?

Dr. CLIFFORD. I still—yes, I mean, it is possible for sure.

Mr. DINGELL. Dr. Khan.

Admiral KHAN. Yes, sir, and there is currently ample evidence that use of antibiotics in animals results in resistant bacteria in food animals, resistance is present in the food supply and transmitted to humans and that resistant bacteria result in adverse human health effects. So that data already exists and is summarized in various documents.

Mr. DINGELL. Now, gentlemen, again, based on this interpretation, and this is to Dr. Sharfstein, based on this interpretation, since 2003 FDA has considered the likelihood for antimicrobial resistance in the drug approval process. Is that correct?

Dr. SHARFSTEIN. Yes.

Mr. DINGELL. Now, has the interpretation been applied to all drugs currently on the market as well as new applications for drugs where the manufacturer is seeking access to the market?

Dr. SHARFSTEIN. No, it has just been applied to new drugs coming on, and that is the reasons we would like to do this guidance is addresses some of the issues with the drugs that were already on the market.

Mr. DINGELL. But you are not dealing with those which are already on the market. All right.

Now, why has this interpretation not been used more widely for those drugs that were on the market prior to 2003? Is it for want of authority by Food and Drug?

Dr. SHARFSTEIN. I don't believe it is for want of authority, no.

Mr. DINGELL. Now, Doctor, what are some of the barriers to new antibacterial drug development and what is FDA doing to help spur innovation in this area?

Dr. SHARFSTEIN. I think there are two main barriers to antimicrobial drug development. One of them is the need for clear approval pathways so that companies can design studies that can reach the right endpoints and be approved, and FDA is working very hard to get the science right so we can have those clear approval pathways. There is a meeting by the end of July that will be the next step in that process.

The second major issue is the issue of incentives for antibiotic development because it is expensive to bring drugs to market, and for antibiotics we don't want them to be used that much when they are there so the market isn't that great, so we believe there is a market issue as well as a pathway issue. FDA is supportive of discussions around the market incentive issue but it is a little bit outside of our sphere to really solve that problem.

Mr. DINGELL. Thank you.

Mr. Chairman, I have used more than my time. Thank you.

Mr. PALLONE. Thank you, Mr. Chairman.

Next is the gentlewoman from Illinois, Ms. Schakowsky.

Ms. SCHAKOWSKY. Dr. Sharfstein, I am trying to understand then what the guidance says. Does it say it will only apply to new drugs?

Dr. SHARFSTEIN. No, no. I am sorry. I must have been confused.

Ms. SCHAKOWSKY. Oh, OK.

Dr. SHARFSTEIN. There is a Guidance 152 that only applies to new drugs. I was referring to a guidance that was issued in 2003. I think that was what Chairman Dingell was referring to. This new guidance—one of the reasons that we are issuing this new draft guidance is because the old one doesn't apply to existing drugs. This deals with some of the issues with existing drugs.

Ms. SCHAKOWSKY. This would apply to all antibiotics?

Dr. SHARFSTEIN. All medically important antibiotics.

Ms. SCHAKOWSKY. Right. OK. So we have the FDA, the USDA, the CDC here today. Which agency has lead jurisdiction to ensure

then that the public is not at risk from overuse of antibiotics in livestock feed?

Dr. SHARFSTEIN. I think FDA has regulatory authority over the use of antimicrobials in animals, but we work very closely with our——

Ms. SCHAKOWSKY. That was my next question. So how do you coordinate? Is there some sort of a——

Dr. SHARFSTEIN. Yes, the President's Food Safety Working Group is one of the places that we have had very good discussions. This issue has been presented in a lot of discussions, and then separate from the big group, we have also worked individually. I think Dr. Clifford and the team at FDA were on the phone multiple times, and certainly CDC was within HHS, we are constantly talking to CDC at FDA.

Ms. SCHAKOWSKY. The FDA voluntary guidelines address non-therapeutic use, right?

Dr. SHARFSTEIN. It addresses what we call production uses, growth promotion, feed efficiency.

Ms. SCHAKOWSKY. But I heard that poultry farmers have recently stated that from egg to slaughter, chickens and turkeys always need antibiotics to prevent disease. Now, here is my concern. If you are only talking about non-therapeutic use, what is to prevent farms from re-categorizing the purpose of the antibiotics they give to animals instead of actually ending the overuse?

Dr. SHARFSTEIN. Well, I think you are getting to the concept of prevention, how we would approach preventive uses, and what the guidance, the draft guidance states is that it is not enough for someone to say I think this prevents disease, that is not enough, that our approach to prevention has to be based on evidence, and factors to consider include the evidence of effectiveness, the evidence that such a preventive use is consistent with accepted veterinary practice, evidence that the use is linked to a specific microbial agent, evidence that the use if appropriately targeted and evidence that no reasonable alternatives for intervention exist. So if we were going to look at prevention uses, which we do believe are important, can be important for animal health, we would apply kind of a scientific evidence-based set of criteria to that scenario.

Ms. SCHAKOWSKY. Dr. Khan, are you comfortable with that as well? Because you talked about prevention being the best thing.

Admiral KHAN. Very much, ma'am, and this is also consistent with how we use antibiotics in humans for prevention purposes, so a good example is meningococcus. It is a meningitis, inflammation of the brain. We do use it for prevention, a specific drug for prevention purposes, but it is specific to targeted people who get it. You get the drug twice a day for two days for targeted infection. You don't get it forever, and everybody in the emergency room, for example, doesn't get it.

Ms. SCHAKOWSKY. Let me ask you this. To what extent would it be true to say that the use of antibiotics can be effective in masking unsanitary conditions where livestock is raised? In other words, if you use antibiotics, then you don't have to be quite as precise about the level of cleanliness at places. Is this ever an issue?

Dr. CLIFFORD. Production management with regards to farms and location of animals, that type of thing could be possible but

that is not a good management use of animals and it is not going to lead to their bottom line economically. If they run poor sanitation on a farm and have to use antibiotics to offset that, they are taking away cost and dollars from their operation, and the bottom line with production agriculture, it is economics. I mean, they are raising food and——

Ms. SCHAKOWSKY. But let me—can I ask one quick question?

Dr. Sharfstein, the guidance has no enforcement component. How can we be sure that it will have any effectiveness at all?

Dr. SHARFSTEIN. Well, the way we think of this is not much as a guidance or regulatory document, this we kind of put out as a white paper. This is sort of the foundation for how FDA intends to move in this area, and then it is basically like a foundation for us to build on. We have had some productive discussions with the various components of the animal agriculture industry and we expect that we will be seeing movement in this direction by their good efforts and I think their comments in response to the guidance indicate that, but I also think that as we move forward under this kind of framework, we will be open to the idea that we will then have to, you know, consider regulatory options. So this was not intended as a regulatory document. It was really intended as a here is what the science says, here is the right direction to move in, and really let us get comments on how to do this as well as possible with the minimal impact on agriculture and let us do it effectively, but we are going to see what we can get from setting this vision and then we are going to consider other things.

Ms. SCHAKOWSKY. This is really a health hazard. It all sounds real slow but I hope that we will have a progress report that will show some movement before too long. Thank you.

Thank you, Mr. Chairman.

Mr. PALLONE. Thank you.

The gentlewoman from the Virgin Islands, Ms. Christensen.

Mrs. CHRISTENSEN. Thank you, Mr. Chairman, and thank the panelists. I really thought I had missed this first round of questioning with the panel but I am glad I didn't.

Just maybe three questions. Dr. Sharfstein, welcome back.

Dr. SHARFSTEIN. Thank you.

Mrs. CHRISTENSEN. The FDA should now be implementing and receiving—I apologize if this question was asked—and receiving more detailed animal drug sales data under the Animal Drug User Fee Act Amendments that was signed into law in 2008. Has any data started coming in?

Dr. SHARFSTEIN. Yes, we have started to get data.

Mrs. CHRISTENSEN. I am concerned that we don't seem to have a method in this country to track actual usage of these drugs in animals that become food. Is that concern warranted, and if so, when would be able to review an analysis of this new data to see whether additional reporting requirements might be necessary?

Dr. SHARFSTEIN. Well, first, we are starting to pull together the data. We are just getting—I don't think we have a complete set yet. I am not 100 percent sure about that, but I know that we are just sort of pulling it together, and I don't think it will be too long before we will be able to share some of that information. But I think to your point, I think you are exactly right. The data under

ADUFA is just part of it. It is overall sales and a little bit by particular use, but it doesn't really tell you how the antimicrobials are being used. It is not the kind of data, for example, that we might get about pediatric practice and pediatricians' use of antimicrobials, and so I think that one of the things that we have been talking about, and there is a meeting very shortly in NARMS coming up is that there is a need for a better surveillance system and that is something where we hope to work very closely with USDA on.

Mrs. CHRISTENSEN. Thank you.

Dr. Khan, we talked a lot about the antibiotic resistance in animals and the fact that it creates resistance in humans but how do people become exposed to antibiotic-resistant bacteria through the food supply? Is it by eating contaminated meat and poultry or can cross-contamination become a problem? And does cooking resolve the problem? Could you just clarify for us how that happens?

Admiral KHAN. Yes, ma'am, I would be glad to. There are multiple mechanisms by which resistant bacteria in animals can make their way into humans. The first is the most obvious. That would be the direct transmission or the direct route, and that would be directly from animals to humans, and we see that——

Mrs. CHRISTENSEN. Just from contact working with animals?

Admiral KHAN. Direct contact, and we see that reported all the time. The second mechanism within that direct route is from food, so contamination of food that subsequently you are handling and you become infected. So we see that route as the direct route. There is also the indirect route of transmission, and this is where specific genetic material within a bacteria of animals can move into bacteria of humans and that resistance, so although the bacteria in animals doesn't move to humans, the resistant pattern moves into humans and then can cause human resistant bacteria.

Mrs. CHRISTENSEN. Thank you for that clarification.

And Dr. Clifford, if funds were available, would the USDA be willing to initiate a pilot program where producers could receive assistance for transitioning to antibiotic-free methods and where results could be collected and reported?

Dr. CLIFFORD. I think one of the issues that is out there is the lack of evidence of cause and effect when you remove these things, so I think it would be important to look at some of these types of things from the standpoint of a pilot project but also from the standpoint of the development of other methods and working with industry and such as vaccine development and other technologies to be able to better address this issue.

Mrs. CHRISTENSEN. So do you have other priorities such as vaccines? New vaccines would be a higher priority than——

Dr. CLIFFORD. I am not saying which one would be the highest priority but I think all those things need to be looked at, and I think we as a body within the federal agencies need to be identifying, sitting down and working with the industry and others to identify the highest priorities and identify the way that we can best use our resources to address those.

Mrs. CHRISTENSEN. In your testimony, you say that animal impacts must be considered in the context of the decision-making

process. Does that mean that there is some tension between USDA and FDA over the approach or are you all on the same page?

Dr. CLIFFORD. Well, I think in general concept, we are on the same page. I mean, it is not that FDA and USDA are going to agree on every particular issue. I think it is important to note that as we all know, this is an extremely complex issue. My role as chief veterinary officer is the protection of animal health. Obviously I care very much about public health as well. So I think we have got to look at all of these things and balance these things, and this is a very complex issue and we don't believe that one size fits all.

Mrs. CHRISTENSEN. Thank you for your answers.

Thank you, Mr. Chairman.

Mr. PALLONE. Thank you, Ms. Christensen.

Thanks a lot. Unfortunately, we are interrupted with two sets of votes today but I appreciate your bearing with us and also changing the date which we did on you a few weeks ago, so this is very helpful. Now, we will likely send additional questions in writing within the next 10 days or so, but I appreciate your being here today. Thanks so much.

Marathon panel coming up here. Let me welcome the second panel. I hope you have enough room there kind of squeezed in. Let me introduce each of you. Starting on my left is Dr. Per Henriksen, who is Head of the Division for Chemical Food Safety, Animal Welfare and Veterinary Medicinal Products from the Danish Veterinary and Food Administration. And then we have Dr. James R. Johnson, Director of Infectious Disease Fellowship Program and Professor of Medicine at the University of Minnesota; Dr. Gail R. Hansen, who is Senior Officer for the Human Health and Industrial Farming Group of the Pew Charitable Trust; Dr. Christine Hoang, who is Assistant Director, Scientific Activities Division for the American Veterinary Medical Association; Dr. Randall Singer, Associate Professor of Epidemiology, Department of Veterinary and Biomedical Sciences, also from the University of Minnesota; Dr. Richard Carnevale, Vice President, Regulatory, Scientific and International Affairs from the Animal Health Institute; and Dr. Stuart Levy, who is Professor of Molecular and Microbiology and Professor of Medicine at Tufts University.

As you know, we ask each of you to limit your comments to 5 minutes, and then of course you can submit additional written comments as well, and we will start with Dr. Henriksen.

STATEMENTS OF PER HENRIKSEN, D.V.M., PH.D., HEAD OF DIVISION, DIVISION FOR CHEMICAL FOOD SAFETY, ANIMAL WELFARE AND VETERINARY MEDICINAL PRODUCTS, DANISH VETERINARY AND FOOD ADMINISTRATION; JAMES R. JOHNSON, M.D., F.I.D.S.A., F.A.C.P., PROFESSOR OF MEDICINE, UNIVERSITY OF MINNESOTA, AND FELLOW, INFECTIOUS DISEASES SOCIETY OF AMERICA; GAIL R. HANSEN, D.V.M., M.P.H., SENIOR OFFICER, HUMAN HEALTH AND INDUSTRIAL FARMING GROUP, PEW CHARITABLE TRUSTS; CHRISTINE HOANG, D.V.M., M.P.H., C.P.H., ASSISTANT DIRECTOR, SCIENTIFIC ACTIVITIES DIVISION, AMERICAN VETERINARY MEDICAL ASSOCIATION; RANDALL SINGER, D.V.M., M.P.V.M., PH.D., ASSOCIATE PROFESSOR OF EPIDEMIOLOGY, DEPARTMENT OF VETERINARY AND BIOMEDICAL SCIENCES, COLLEGE OF VETERINARY MEDICINE, DIVISION OF EPIDEMIOLOGY, SCHOOL OF PUBLIC HEALTH, UNIVERSITY OF MINNESOTA; RICHARD CARNEVALE, D.V.M., VICE PRESIDENT, REGULATORY, SCIENTIFIC AND INTERNATIONAL AFFAIRS, ANIMAL HEALTH INSTITUTE; AND STUART LEVY, M.D., PROFESSOR OF MOLECULAR AND BIOLOGY, PROFESSOR OF MEDICINE, TUFTS UNIVERSITY

STATEMENT OF PER HENRIKSEN

Dr. HENRIKSEN. Thank you, Mr. Chairman, Mr. Ranking Member and members of the subcommittee for inviting me to testify. First I can say I am a veterinarian by training, got my degrees from Royal Veterinary and Agriculture University of Copenhagen, Denmark. I have been working as a scientist for more than 10 years. I have been working in the farmers' organization as a health consultant for more than 5 years and working for the Danish government for more than 10 years.

As a representative of the Danish government, I am aware that the use of antibiotic growth promoters is a contentious issue in the United States and that Denmark is often mentioned in the debate. Against this background, I wish to emphasize that the Danish government is not represented here today to advocate for or against any specific legislative proposals. However, we are a nation willing to share our experiences when requested and therefore we have accepted your kind invitation.

I submitted five fact sheets for the record, and with the subcommittee's indulgence, I will therefore shorten my remarks to allow for your questions.

Mr. PALLONE. I want to interrupt and say that I understand you obviously came from Denmark here today to participate in this hearing, and we really appreciate your coming so far to be with us today. Thank you.

Dr. HENRIKSEN. Thank you.

Denmark is a major livestock producer in Europe and the world's largest exporter of pork. Danish livestock production is highly industrialized, intensive and supplies modern management principles. Due to the significance for the Danish economy, the Danish government takes the competitiveness of the Danish farmers seriously.

Treatment with antibiotics is in many cases essential for human and animal health and an uncritical use of antibiotics can lead to several antibiotics becoming ineffective. Because antimicrobial resistance can be transferred between bacteria, regardless of whether the bacteria are pathogenic or not, the development of antimicrobial resistance in any kind of bacteria can constitute a problem.

It is a fact that antimicrobial resistance can be transferred from animals to humans by consumption of meat, and every year also Denmark experience human outbreaks caused by consumption of meat contaminated with resistant bacteria.

A ban on antimicrobial growth promoters was considered necessary for several reasons in Denmark. There was science-based evidence that the use of antibiotics in animal feed could create resistance in pathogenic bacteria to medically important antibiotics, and there was a real concern that doctors would run out of options for treating life-threatening infections in humans. Given the fact that very recently, a Danish Ph.D. project concluded that production animals and meat might be a source of human E. coli urinary tract infections, the Danish ban seemed to be an example of due diligence.

Among the initiatives that are all mandated by the Danish government, I would like to mention the following: No prophylactic use of antimicrobials and mandatory low fixation of the veterinarians' profit from sales of medicine. This fixation of low profit was an initiative of the Danish Veterinary Medical Association. The critically important antibiotics call fluoroquinolones can only be used in Denmark if a laboratory test shows that no other antibiotics can be used. Treatment guidelines for swine and cattle veterinary practitioners have been issued by the government. Continuous monitoring and research in antimicrobial resistance in animals, humans and food. Monitoring of foodborne pathogens in Danish as well as imported meat. Antimicrobial resistance is one of the parameters used to determine whether a shipment of imported food is dangerous or not. Control and action plans to combat Salmonella bacteria in poultry and pork and Campylobacter in poultry are implemented. And the most recent development includes mandatory action plans in swineherds above a certain threshold value for antibiotic use, the so called "yellow card."

It is important to note that, according to our experience, a ban on antibiotic growth promoters can immediately and dramatically reduce the amount of antibiotics used. In Denmark the decrease was 40 percent. Such a ban should not stand alone in the long run. This explains the fact that we have implemented this range of follow-up measures and we can expect also to have to take additional steps in the future.

The ban of growth promoters has resulted in a marked reduction in antimicrobial resistance as measured among several different bacterial species in food animals. The percentage of macrolide resistance in porcine Campylobacter has decreased from 80 percent before the ban to less than 20 percent in 2006. A similar reduction from more than 75 percent vancomycin resistance in enterococci isolated from broilers before the ban to less than 5 percent.

Additionally, Denmark has a markedly lower level of resistant bacteria in meat compared to meat imported from other EU member states. I can mention as an example, that the percentage of cephalosporin resistance in E. coli isolated from Danish broilers' meat is less than 5 percent, while more than 35 percent of E. coli isolated from broiler meat from other EU member states reveals cephalosporin resistance. This marked difference in resistance can be ascribed to our ban of growth promoters and low usage of antimicrobials compared to other EU countries.

The Danish swine industry has been producing pigs without the use of growth promoters for many years now and has increased both the production and the productivity. The same picture applies in the broiler chicken and cattle industries. In the last few years, and particularly in 2009, we have noted an increase of usage of antimicrobials above the concurrent increase in pig production. However, as this increase appears more than 10 years after the ban, we do not relate this to the ban. Nevertheless, we take this recent increase in usage seriously and have imposed several initiatives.

When presenting the Danish experience here in the United States, it is important to stress that Denmark is favored by a range of institutional characteristics which helped implementing the ban and the following steps. In Denmark, we can identify every herd, farmer and veterinarian and we are able to pinpoint the antimicrobial usage right down to the individual cow and to an age group of swine. This is due to our many databases on husbandry and medicine usage. And we have also monitored and researched in resistance for the past 15 years in a program called DANMAP. Our farming industry is highly organized in a cooperative structure with one common organization for farmers and food companies. We have a longstanding tradition for working towards a consensus between government, industry and the Danish Veterinary Medical Association. I would like to mention that the Danish Veterinary Medical Association along with the Danish Medical Association has supported a ban from the beginning.

Working as an entity, the Danish swine industry has therefore played an important role and voluntarily stopped all non-therapeutic use of antibiotics starting in 1998, with a total state ban in place by January 2000. Only 2 weeks ago the Danish swine industry again issued a voluntary ban, this time against therapeutic treatment with the critically important antibiotic cephalosporin. Danish farmers are well educated and have easily learned to produce pigs without growth promoters. Instead, they use good management, weaning at 28 days instead of 21 days, initiatives concerning food and proper care of sick animals. These institutional advantages have enabled Denmark to take ambitious risk-mitigating strategies in order to combat antimicrobial uses and resistance and without endangering the economic sustainability of the swine industry.

If you have any questions, I will gladly answer them, and I will also your attention to the fact sheet handed out. Thank you for your attention.

[The prepared statement of Dr. Henriksen follows:]

Ministry of Food, Agriculture and Fisheries
Danish Veterinary and Food Administration

CHECK AGAINST DELIVERY

12 July 2010

Danish testimony on the July 14th Hearing about Antibiotic Resistance in the Livestock Industry organised by the Subcommittee on Health

By Per Henriksen, DVM, PhD, Head of Division for Chemical Food Safety, Animal Welfare and Veterinary Medicinal Products, The Danish Veterinary and Food Administration

Thank you, Mr. Chairman, Mr. Ranking Member, and Members of the Subcommittee, for inviting me to testify.

As a representative of the Danish government I am aware that the use of antibiotic growth promoters is a contentious issue here in the US and that Denmark is often mentioned in the debate. Against this background I wish to emphasize that the Danish government is not represented here today to advocate for or against any specific legislative proposals. However, we are an open nation, willing to share our experience when requested and therefore we have accepted your kind invitation.

I have submitted five fact sheets for the record, and with the Subcommittee's indulgence, I will therefore shorten my remarks to allow for your questions.

.....

Denmark is a major livestock producer in Europe, and the worlds' largest exporter of pork. The Danish livestock production is highly industrialised, intensive and applies modern management principles. Due to the significance for the Danish economy the National Government takes the competitiveness of the Danish farmers seriously.

Treatment with antibiotics is in many cases essential for human and animal health and an uncritical use of antibiotics can lead to several antibiotics becoming ineffective.

Because antimicrobial resistance can be transferred between bacteria, regardless of whether the bacteria are pathogenic or not, the development of antimicrobial resistance in any kind of bacteria can constitute a problem.

It is a fact that antimicrobial resistance can be transferred from animals to humans by consumption of meat and every year also Denmark experience human outbreaks caused by consumption of meat, contaminated with antimicrobial resistant bacteria.

A ban on antimicrobial growth promoters was considered necessary for several reasons: There was science-based evidence that the use of antibiotics in animal feed could create resistance in pathogenic bacteria to medically important antibiotics, and there was a real concern that doctors would run out of options for treating life-threatening infections in humans.

Given the fact that very recently, a Danish PhD project concluded that production animals and meat might be a source of human E. coli urinary tract infections, the Danish ban seemed to be an example of due diligence.

.....

Among the initiatives, that are all mandated by the Danish government, I would like to mention the following:

- No prophylactic use of antimicrobials and mandatory low fixation of the veterinarians profit from sales of medicine.

- The critically important antibiotics fluoroquinolones can only be used, if a laboratory test shows, that no other antibiotics can be used.

- Treatment guidelines for swine and cattle veterinary practitioners have been issued.

- Each individual veterinary practitioner is subjected to risk management and risk communication on prudent and reduced usage of antibiotics.

- Continuous monitoring and research in antimicrobial resistance in animals, humans and food.

- Monitoring of food borne pathogens in Danish as well as imported meat. Antimicrobial resistance is one of the parameters used to determine whether a shipment of food is dangerous.

- Control and action plans to combat Salmonella bacteria in poultry and pork and Campylobacter in poultry are all implemented

And the most recent development includes mandatory action plans in swineherds above a certain threshold value for antibiotics usage – the so called 'yellow card' initiative.

It is important to note that, according to our experience, a ban on antibiotic growth promoters can immediately and dramatically reduce the amount of antibiotics used. In Denmark the decrease was 40%. But such a ban should not stand-alone in the long run. This explains the fact that we have implemented this range of follow up measures and we expect also to have to take additional steps in the future.

.....

I would now briefly present some results of the initiatives:

The ban of growth promoters has resulted in a marked reduction in antimicrobial resistance as measured among several different bacterial species in food animals. The percentage of macrolide resistance in porcine Campylobacter has decreased from 80% before the ban to less than 20% in 2006. A similar re-

duction from more than 75 % vancomycin resistance in enterococci isolated from broilers before the ban to less than 5% in 2006.

Additionally, Denmark has a markedly lower level of resistant bacteria in meat compared to imported meat from other EU member states. I can mention as an example, that the percentage of cephalosporin resistance in E. coli isolated from Danish broiler meat is less than 5%, while more than 35% of E. coli isolated from broiler meat from other EU-member states reveal cephalosporin resistance. This marked difference in resistance can be ascribed to our ban of growth promoters and low usage of antimicrobials compared to other EU countries. According to data from the European Food Safety Authority the total consumption of antimicrobials in food producing animals in 2007 was 120 metric tons in Denmark and almost 600 metric tons in another EU country with a comparable type of pig production.

The ban of growth promoters came into force in 1995 and we noted a substantial decrease of 40% in the consumption of antibiotics in the years thereafter.

The Danish swine industry has been producing pigs without the use of growth promoters for many years now and has increased both the production and the productivity. The same picture applies in the broiler chicken and cattle industries.

15 years after the ban the overall amount of antibiotics used for animals in Denmark is still almost 40% below the pre-ban level. As some US observers has pointed out, there has been an increase in the consumption of antimicrobials for therapeutical use during the post-ban years, but it has to be remembered, that the pig production has increased 25% in the same period, which can account for more than the increase in consumption of antimicrobials.

In the last few years and particularly in 2009 we have noted an increase of usage of antimicrobials above the concurrent increase in pig production. However, as this increase appears more than 10 years after the ban of growth promoters, we do not relate this to the ban. Nevertheless, we take this recent increase in usage seriously and have imposed the above-mentioned recent initia-

tive - the 'yellow card' where farms using antibiotics above a certain threshold are mandated to reduce their use.

Salmonella levels have been between 0-2 % in eggs and chicken, and the Salmonella level in pork has remained low.

.....

When presenting the Danish experience here in the US, it is important to stress that Denmark is favoured by a range of institutional characteristics which helped implementing the ban and the following steps.

- In Denmark we can identify every herd, farmer and veterinarian and we are able to pinpoint the antimicrobial usage right down to the individual cow and to an age-group of swine. This is due to our many databases on husbandry and medicine usage. And we have also monitored and researched in resistance for the past 15 years in a targeted program called DANMAP.

- Our farming industry is highly organised in a co-operative structure with one common organisation for farmers and food companies. We have a longstanding tradition for working towards a consensus between government and industry and this was also the case with the ban on antimicrobial growth promoters.

- Working as an entity, the Danish swine industry has therefore played an important role and voluntarily stopped all non-therapeutic use of antibiotics, starting in 1998, with a total state ban in place by January 2000. Only two weeks ago the Danish swine industry again issued a voluntary ban; this time against therapeutic treatment with the critically important antibiotic Cephalosporin.

- Danish farmers are well educated and have easily learnt to produce pigs without antibiotic growth promoters. Instead they use good management,

weaning at 28 days, initiatives concerning feed and proper care of sick animals.

Thus, institutional advantages have enabled Denmark to take ambitious risk mitigating strategies in order to combat antimicrobial usage and resistance – and without endangering the economic sustainability of the swine industry.

.....

In conclusion Denmark can state the following results:

- Antimicrobial resistance is reduced after the ban
- Total antibiotic consumption in food producing animals has been reduced by almost 40% from the mid 1990's till today
- Animal health has not been compromised
- Agricultural productivity has continued to improve
- The farmer's economy has not been significantly threatened
- Food safety in Danish products of animal origin has significantly improved as regards specifically Salmonella and Campylobacter
- A range of institutional factors helped Denmark implement the ban
- A ban on antibiotic growth promoters can be a very substantial and fulfilling first step in combating antimicrobial resistance, but should not stand alone in the long run

If you have any questions I will gladly answer them, and I will also direct our attention to the fact sheets handed out. Thank you for your attention.

Ministry of Food, Agriculture and Fisheries
Danish Veterinary and Food Administration

12 July 2010

FACT SHEETS

On the Danish restrictions of non-therapeutical use of antibiotics for growth promotion and its consequences

Denmark is a major livestock producer in Europe, and the worlds' largest exporter of pork. The Danish livestock production is highly industrialised, intensive and applies modern management principles. Due to the significance for the Danish economy the National Government takes the competitiveness of the Danish farmers seriously.

The Danish initiatives in the area of non-therapeutic use of antibiotics for growth promotion and control of the use of therapeutic antibiotics were – and still are - all taken to reduce the risk for occurrence of resistant bacteria in the food chain.

To provide facts on the background for the initiatives taken, the initiatives themselves, and our results The Danish Veterinary and Food Administration has developed five FACT SHEETS:

I. General data on the Danish agricultural sector
II. The Danish initiatives taken to mitigate the risk of resistant bacteria in the food chain
III. The occurrence of resistant bacteria in herds, in food of animal origin, and in humans
IV. Effects of the initiatives to reduce the use of antibiotics
V. Concurrent development with regard to food borne pathogens in food of animal origin

FACT SHEET I

General data on Danish agriculture

Denmark

Denmark lies between 54° and 58° of latitude north and 8° and 15° of longitude east. It is neighbouring Germany to the South, the North Sea to the West, Sweden to the East and Norway to the North. In addition to Denmark itself, the Kingdom also includes the Faroe Islands and Greenland.

- Population: 5.511.451 (2010)
- Area: 43.098 square kilometres
- Population density: 126,4 pr. square kilometre
- Geographic region: Scandinavia
- Gross domestic product: Approximately 280 billion USD (2009)

(The Ministry of Foreign Affairs in Denmark)

Agriculture

- The Danish agricultural sector in combination with the food industry employs some 150.000 persons and represents an export value of approximately 17 billion USD
- In 2008 approximately 5.800 pig farms, 5.200 dairy farms and 300 with specialised poultry production
- Census data 2008: 558.000 dairy cows (1.6 million cattle in total), 12.7 million pigs and 3.5 million hens
- Highly specialised – only 3% has more than one animal species
- Highly co-operatively organized sector where farmers own their slaughtering and processing companies
- Large co-operative companies including *Danish Crown*, the world's largest exporter of pork, with a group turnover at approximately 7.5 billion USD, and the dairy food company *Arla Foods* with a group turnover at approximately 7.8 billion USD
- Farmers, co-operatives and most private companies in the Danish agricultural sector are part of the same joint organisation: Danish Agricultural and Food Council

(Danish Agricultural and Food Council)

FACT SHEET II
The Danish initiatives to mitigate the risk of

resistant bacteria in the food chain

EU and Danish government interventions

- Since before the 1970s all veterinary medical products have been prescription only
- In 1994 the Central Husbandry Register (National Animal Identification System) was established, with national registration and identification of every herd in Denmark
- In 1994/95 any prophylactic use of antimicrobials was prohibited and the veterinarians' profits from direct sales of medicine were fixated at a very low level with a maximum of 10%
- In 1995 preventive veterinary strategies were implemented with herd health contracts on a voluntary basis and regular monthly visit from the veterinarian, irrespective of the actual herd health situation, in order to promote preventive veterinary strategies, optimizing antimicrobial use
- In 1995 the DANMAP programme (Danish Antimicrobial Resistance Monitoring and Research Programme, www.DANMAP.org) was established. The programme monitors and does research on antimicrobial usage and resistance in humans, animals and food and involves scientists, risk analysists and risk managers within both human and animal health
- In 1995, the Danish government banned the non-therapeutic use of avoparcin for growth promotion in Denmark; a ban that was extended to all EU countries in 1997.
- In January 1998, the Danish government banned the non-therapeutic use of virginiamycin for growth promotion.
- In December 1998 the EU implemented an overall ban of virginiamycin, bacitracin, tylosin and spiramycin for growth promotion.
- In 2000 the medicine database VetStat was established, recording every antibiotic prescribed to production animals on the age-group and herd and veterinarian level
- In 2002 fluoroquinolones were restricted to only be used if a current laboratory test shows that no other antibiotics can be used for that disease in that herd of production animals

- In 2002, EU voted to phase out all non-therapeutic use of antibiotics for growth promotion (i.e. all non-prescription use) as of the beginning of 2006.

- From 2003 the Medicine Control Task Force, a special unit under the Danish Veterinary and Food Administration, was established. The special unit plans the risk-based control and assists the regional veterinary officers in difficult cases; the unit assists the police and the Prosecution.

- Action plan 2005 for reduction and prudent use of antimicrobials in swine, including

    - treatment guidelines for swine veterinary practitioners
    - direct risk communication with the individual swine veterinary practitioners with a high prescription rate.

- Action plan 2007 for reduction and prudent use of antimicrobials in cattle, swine and poultry, including
    - direct risk communication including audit and supervision of prudent use of antimicrobials, every second year, of **all veterinarians working with food-producing animals**
    - a task force was established between the Danish Medicines Agency, the Danish Veterinary and Food Administration and taxation authorities in order to secure that there are no economical relationships between veterinary practitioners and the pharmaceutical industry
    - treatment guidelines for cattle veterinary practitioners.

- From 2009 an Early Notification Board on antibiotic usage in swine and cattle in cooperation with the industry, the Danish Veterinary Association and the Danish Veterinary and food Administration.

- From 2010 evidence based – including pharmacokinetics and –dynamics - novel treatment guidelines for swine veterinary practitioners

- From 2010 a joint Antimicrobial and Resistance action plan between the Ministry of Health and the Ministry of Food, Agriculture and Fisheries.

- From 2010 a National Antimicrobial Board for reduction of antimicrobial use and resistance with representatives from the Danish Veterinary and Food Administration, The Danish National Board of Health and scientists from both veterinarian and human health.

- From 2010 non-voluntary herd health agreements for swine and cattle with emphasis on health prevention strategies and animal welfare reducing antibiotic usage and resistance

- From 2010 establishment of threshold values for acceptable herd levels on mortality, antibiotic usage and certain welfare parameters in swine and cattle and enforced control in herds with levels above the threshold values

- From 2010 mandatory action plans for reduction of antibiotic usage in swine herds above the threshold value for antibiotics usage – the so-called 'yellow card' initiative

Voluntary actions taken by the Danish agricultural industry

- The Danish cattle and broiler industries voluntarily stopped the non-therapeutic use of all antibiotics for growth promotion in February 1998.

- The Danish swine industry voluntarily stopped all non-therapeutic use of antibiotics in swine above 35 kg by April 1998, and for all age groups by January 2000.

- The Danish swine industry enforced a voluntary ban on all usage of the high-risk antibiotics Cephalosporins from 1. July 2010.

All the Danish agricultural industries initiatives were taken voluntarily and upon their own initiative and had nothing to do with any orders or fines from the authorities. Presumably, the industry found it worthwhile to have a production free from antimicrobial growth promoters, very low antimicrobial residues and a high standard on food safety.

FACT SHEET III

The occurrence of resistant bacteria in herds, food of animal origin and in humans

Risk of transmitting antimicrobial resistance from animals/food to humans

- Cephalosporin usage is for instance causing resistance in Escherichia coli (E. coli). This is shown, as prevalence of ESC positive E. coli from Danish farms with and without Cephalosporin consumption <6 month prior to sampling, shows that farms without Cephalosporin usage has only 8% ESC positive E.coli compared to 18% in herd using Cephalosporins.. ESC is a group of genes coding for resistance against 3. and 4. generation Cephalosporins. (Y. Agersø, DTU, 2010)
- Studies from 2009 detected ESC positive E. coli in 35 % of the samples from imported broiler meat (3.4% Danish broiler meat) (Figure 1) (Y. Agersø, DTU, 2010)

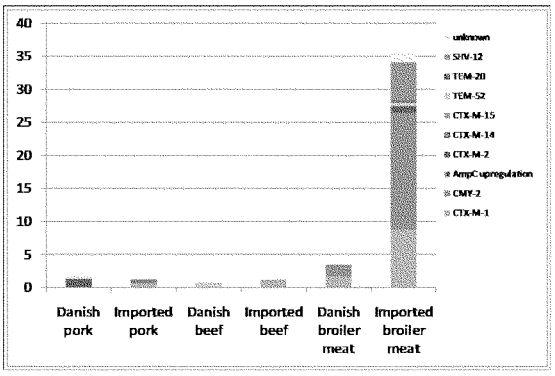
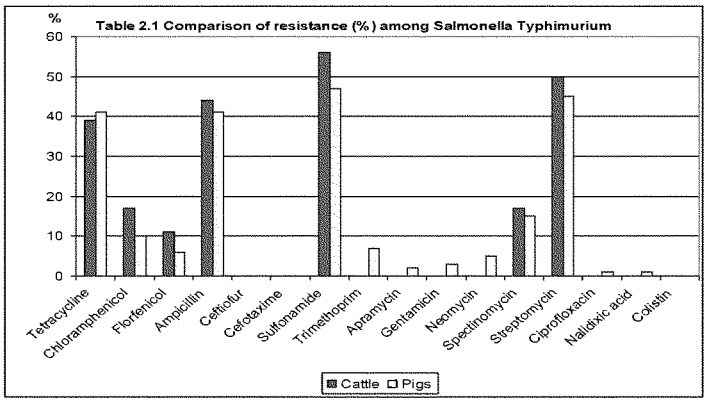


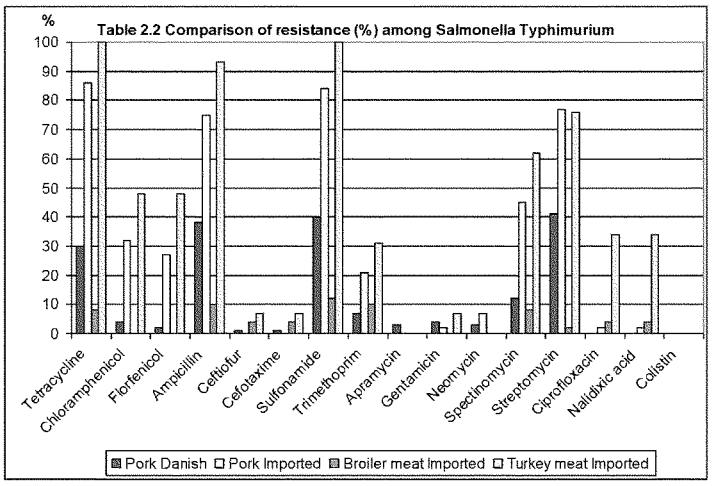
Figure 1: % Ceftriaxone resistant *E. coli* in each of six meat categories and distribution of ESC genes.

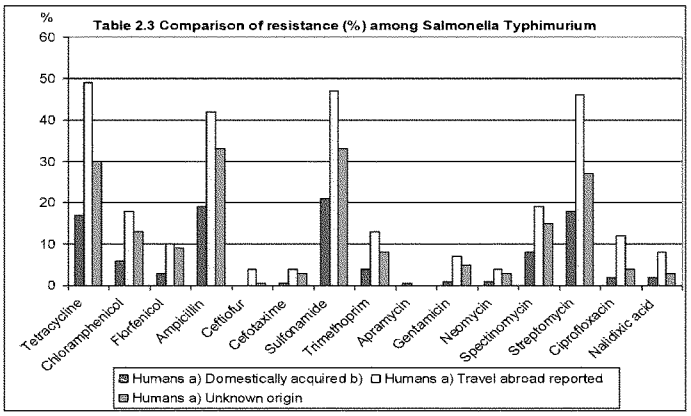
Antibiotic resistance in zoonotic and other bacteria

- Resistance in Salmonella Typhimurium in Danish animals and products, in imported products and in humans. For humans, the principal source is indicated. (Table 2) (DANMAP 2008). Shows the amount of resistance in imported meat is much higher and resistance in humans are often acquired abroad.

Table 2.1 – 2.3. Comparison of resistance (%) among Salmonella Typhimurium from food animals, pork of Danish and imported origin and human cases acquired domestically a), reported as associated with travel abroad or with an unknown origin, 2008







- Resistance in Campylobacter jejuni from food animals, food of Danish or imported origin and human cases categorized as acquired domestically or reported as associated with travel abroad 2008 (Table 3) (DANMAP 2008). Shows that resistance in broiler meat is mainly imported and for a large proportion acquired abroad for humans. Pork and swine not in the table, as Campylobacter in swine in Denmark most often are C. coli.

Table 3. Comparison of resistance (%) among Campylobacter jejuni from food animals, food of Danish or imported origin and human cases categorized as acquired domestically or reported as associated with travel abroad 2008

Compound	Cattle	Broilers	Broiler meat		Humans	
	Danish	Danish	Danish	Imported	Domestically acquired	Travel abroad reported
	%	%	%	%	%	%
Tetracycline	3	10	12	49	17	51
Chloramphenicol	0	0	0	0	0	0
Erythromycin	0	0	0	7	2	7
Gentamicin	0	0	0	0	2	2
Streptomycin	1	5	4	3	2	15
Ciprofloxacin	20	12	19	53	28	73
Nalidixic acid	20	12	19	53	29	73
Number of isolates	90	82	26	152	185	41

Resistance in Escherichia coli from food animals, food of Danish and imported origin and army recruits, 2008 (Table 4) (DANMAP 2008)

Table 4. Occurrence of resistance (%) among Escherichia coli from food animals, food of Danish and imported origin and army recruits, 2008

Compound	Broilers	Cattle	Pigs	Broiler meat		Beef		Pork meat		Army recruits
	Danish	Danish	Danish	Danish	Imported	Danish	Imported	Danish	Imported	
	%	%	%	%	%	%	%	%	%	%
Tetracycline	11	4	30	4	42	5	12	33	44	29
Chloramphenicol	0	1	1	0	14	0	2	6	7	5
Florfenicol	0	1	0	0	1	0	2	0	1	0
Ampicillin	12	1	19	11	48	6	10	29	30	28
Cephalothin	-	-	-	-	-	-	-	-	-	3
Ceftiofur	0	0	0	1	8	0	0	0	1	1
Cefpodoxime	-	-	-	-	-	-	-	-	-	3
Cefotaxime	0	0	0	1	8	0	0	0	1	-
Sulfonamide	11	5	25	12	45	6	15	30	28	35
Trimethoprim	4	2	18	3	32	2	5	24	25	-
Apramycin	0	0	0	0	0	0	0	0	0	0
Gentamicin	1	0	1	0	3	0	0	0	2	7
Neomycin	1	0	3	0	10	0	2	2	6	9
Spectinomycin	3	1	14	6	23	0	5	20	15	11
Streptomycin	8	4	26	8	33	8	15	32	40	28
Ciprofloxacin	12	0	1	4	33	0	5	2	6	13
Nalidixic acid	12	0	1	3	32	0	5	2	4	13
Colistin	0	0	0	0	4	0	0	0	1	-
Number of isolates	114	97	151	113	304	63	40	66	96	75

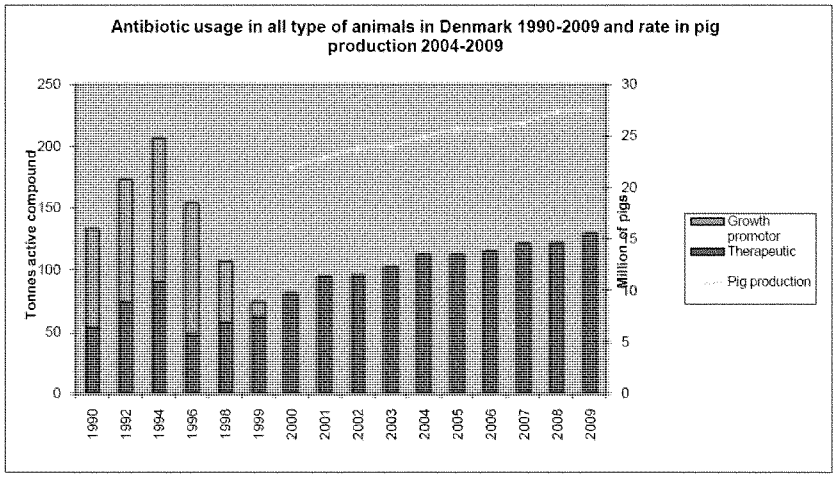
FACT SHEET IV

Effects of the initiatives to reduce the use of antibiotics

Changes in antimicrobial usage in Danish agriculture from 1992 to 2009

- Total antimicrobial consumption in Denmark for all animals (Figure 1) has fluctuated over time; highest in 1994 and lowest in 1999. And the consumption is still 37% less in 2009 than in 1994. The production of pigs has increased continuously over time (The Danish Veterinary and Food Administration, 2010).

Figure 1. Consumption of antibiotics (therapeutic and non-therapeutic (AGP)) in all type of animals in Denmark. Usage in tonnes and pig production in million heads. Swine comprises >80% of all usage in animals.



Changes in antimicrobial resistance

- The stop for use of different non-therapeutic antibiotic growth promoters (avilamycin, avoparcin, spiramycin, tylosin, virginiamycin) has resulted in a reduction in antimicrobial resistance, for instance vancomycin resistance (figure 2) (www.DANMAP.org)

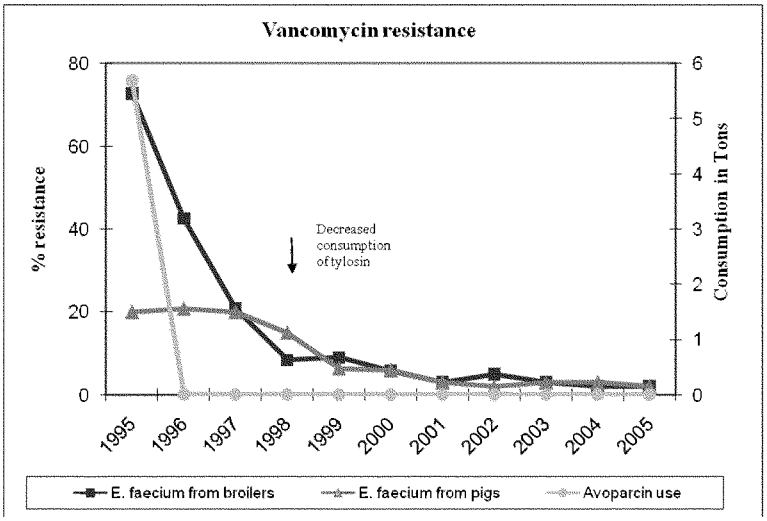


Figure 2. Occurrence of vancomycin resistance and consumption of avoparcin from 1995-2005 - Denmark

- Tylosine is used for both growth promotion and therapy. This usage will also select for (lead to development of) resistance in Campylobacter. As shown in figure 3, the occurrence of macrolide resistance in *Campylobacter coli* from pigs has closely followed the consumption of tylosine in the food animal production (www.DANMAP.org)
- **Campylobacter coli are the absolutely most common Campylobacter in Danish swine. C. jejuni is very rare in swine in Denmark.**

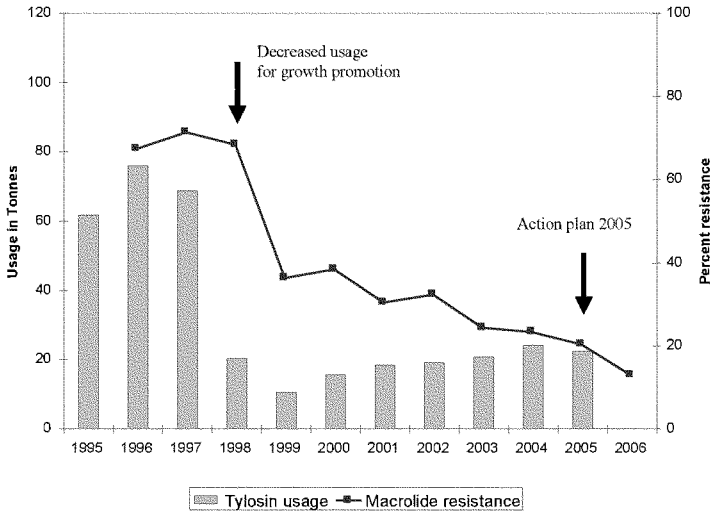


Figure 3. Macrolide resistance among Campylobacter coli from pigs and consumption of tylosine for growth promotion and therapy, 1995-2006, Denmark.

Effects on productivity and animal health - Denmark

Cattle

- No evidence, not even anecdotal, suggests any negative health effects of the growth promoters stop, as there were no increases in treatment of neither sick animals nor mortality.

Swine

- The Danish swine production has increased with similar rates before and after the non-therapeutic use of for growth promotion stopped (almost 50% from 1992 to 2008). Also the average annual number of pigs raised for slaughter per sow has continued to increase (figure 4) (DTU, Danish Technical University, 2009)

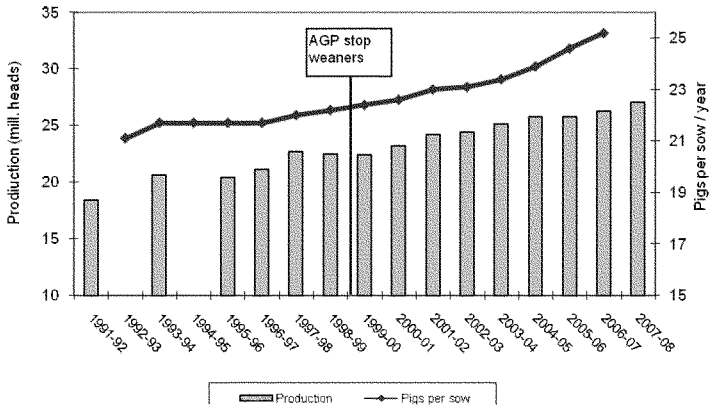


Figure 4. Production of swine and numbers of pigs produced per sow/year in Denmark

- Weaner mortality increased several years before as well as few years after non-therapeutic use stopped, but has drastically decreased in recent years, indicating little if any effect of the termination. Weaner average daily gain has increased after the termination. (Figure 5) (DTU, Danish Technical University, 2009).

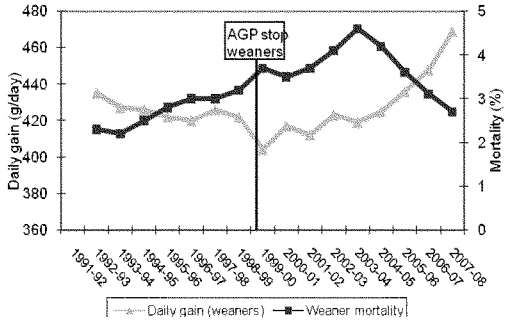


Figure 5. Daily weight gain of weaner pigs and mortality of weaner pigs in Denmark

- Finisher mortality has not been affected by the termination. Finisher average daily gain has continued to increase before and after the termination (Figure 7) (DTU, Danish Technical University, 2009).

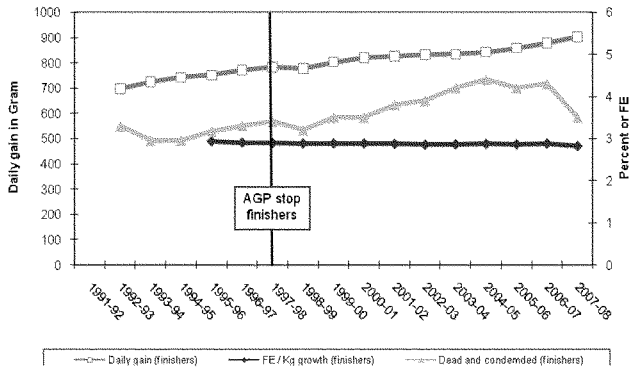


Figure 7. Daily weight gain, mortality and feed efficiency of finishing pigs in Denmark

Broilers

- Productivity and mortality was not affected by the termination, as shown in the figures beneath. Productivity varied both before and after the ban. The feed conversion ratio increased, but the amount spent on feed was gained again as there were no expenses on growth promoters. Productivity is measured not in number of broiler heads, but kg of broilers pr square meter in the stable (Figure 8, 9, 10) (DTU, Danish Technical University, 2009)

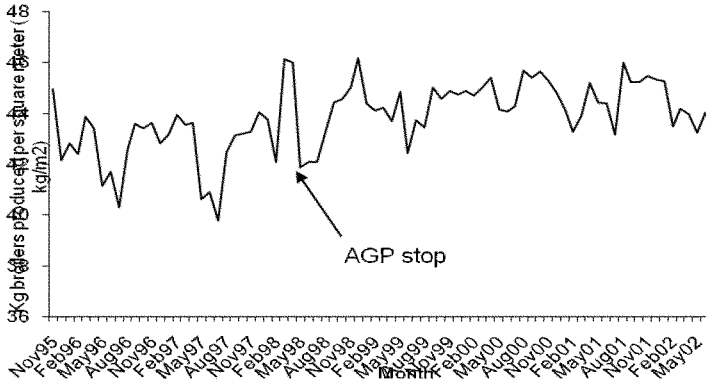


Figure 8. Productivity of broiler chicken in Denmark (kg produced per sqm)

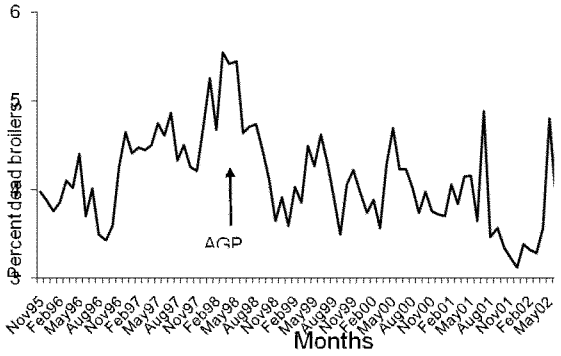


Figure 9. Mortality of broiler chicken in Denmark

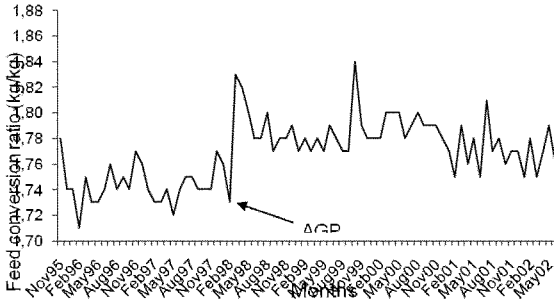


Figure 10. Feed conversion ratio in broilers in Denmark, change offset by reduced costs

FACT SHEET V

Concurrent development with regard to food borne pathogens in food of animal origin

Salmonella in pigs

- Action and control plans have been installed in Denmark since 1995. Prevalence of seropositive pigs in the breeding and multiplying herds is shown in Figure 1, prevalence of seropositive pigs for slaughter in Figure 2, and prevalence of bacteriologically positive carcasses in Figure 3. References for all Figures (Annual Report on Zoonoses in Denmark, DTU, 2009)

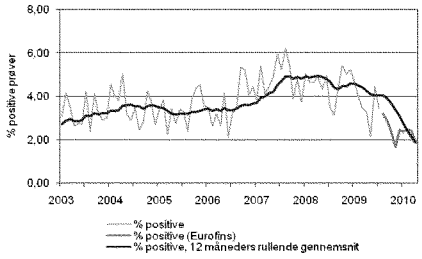


Figure 1. Percent positive samples, breeding and multiplier pigs.

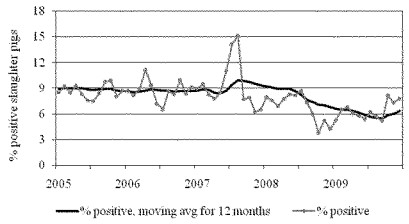


Figure 2. Percentage of positive meat juice samples – slaughter pigs.

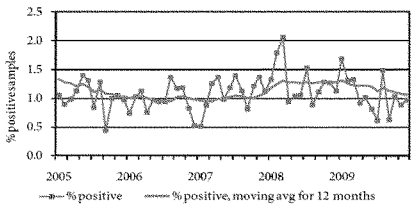


Figure 3 . Percentage of positive carcasses at the slaughterhouse.

Salmonella in layer flocks and in the broiler production

- Action and control plans have been installed in Denmark since the late 1980ies. The occurrence of salmonella in the layer sector (breeding flocks and layer flocks) is shown in Figure 4. Occurrence of salmonella in broilers is shown in Figure 5. Eggs and broilers from contaminated flocks are prevented from entering the market. References for Figures (Annual Report on Zoonoses in Denmark, DTU, 2009)

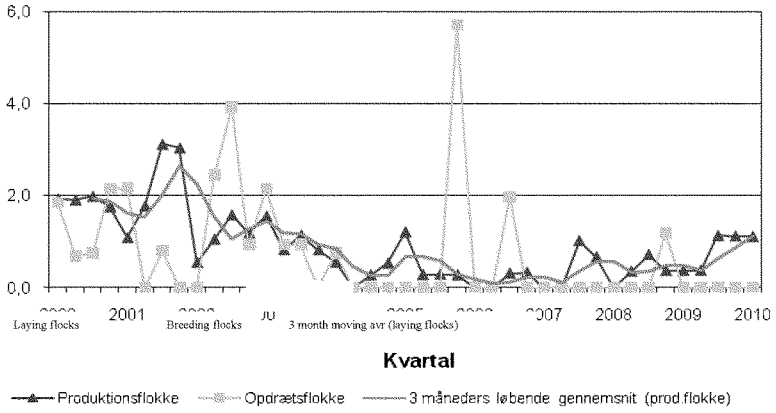


Figure 4. Prevalence (%) of salmonella in Danish table-layer flocks

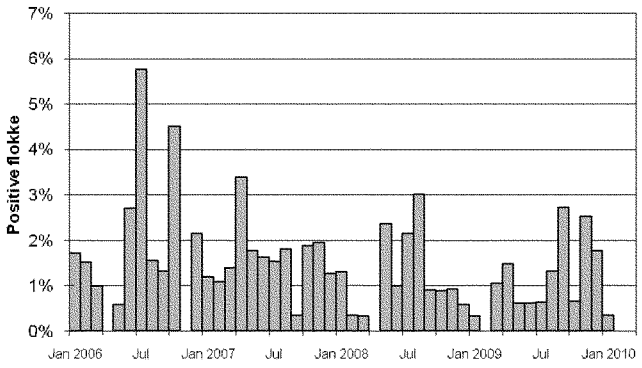


Figure 5. Prevalence of salmonella in Danish broiler flocks

Mr. PALLONE. Thank you, Dr. Henriksen.
Dr. Johnson.

STATEMENT OF JAMES R. JOHNSON

Dr. JOHNSON. Chairman Pallone——
Mr. PALLONE. Could you maybe bring that mic a little closer? I always gave Dr. Henriksen a lot of leeway, since he came from Denmark. The rest of you should try to stick to the 5 minutes. I think you have to either turn it on or move it closer.
Dr. JOHNSON. It was the turning it on. Thank you.
Chairman Pallone, Ranking Member Shimkus and members of the subcommittee, on behalf of the 9,000-plus members of the Infectious Diseases Society of America, or IDSA, I appreciate this opportunity to speak in support of the Health Subcommittee's efforts to promote judicious use of medically important antibiotics in animal agriculture. I am James Johnson, an infectious diseases physician, a Professor of Medicine at the University of Member, and a member of IDSA's antimicrobial resistance work group.
I applaud the emphasis that Ranking Member Shimkus and Congressman Pitts as well as other speakers today have put on science as a foundation and guide for decision-making in this area. I would point out that IDSA is made up of research scientists, infectious disease commissions and public health epidemiologists who value and rely on the scientific method. IDSA supports rigorous science and critical impartial evaluation of the scientific evidence base. IDSA also publishes two of the premier peer-reviewed scientific medical journals in infectious diseases, Journal of Infectious Disease and Clinical Infectious Disease. These two journals have published dozens, if not hundreds, of peer-reviewed scientific studies on this topic.
IDSA supports efforts to eliminate all non-judicious uses of antibiotics in human medicine and agriculture such as the Preservation of Antibiotics for Medical Treatment Act, or PAMTA, and the FDA's recently announced public health approach toward antibiotic use in food animals. The elimination of non-judicious will mean the end of antibiotics for growth promotion, feed and efficiency and routine disease prevention in food animals. The United States also must strengthen efforts to ensure that all other food animal antibiotic use is supervised by a veterinarian within the boundaries of a valid veterinarian-client-patient relationship.
Now, IDSA regards the development of antibiotics to treat life-threatening infections as one of the most notable medical achievements of the past century. Unfortunately, these wonder drugs' ability to cure is being increasingly compromised by emerging antibiotic-resistant pathogen, and there are few new antibiotics in development that will come to our rescue any time soon. As a result, infectious disease physicians and public health experts believe that we must do everything in our power to preserve existing antibiotics to protect both human and animal health.
As noted in opening statements by several committee member including Congressman Murphy and the Administration witnesses, an extensive body of scientific evidence demonstrates that antibiotic use in food animals does contribute to the spread of resistant bacteria to humans, leading to drug-resistant infections with their

many adverse consequences. Our written testimony cites science-based studies and reports from authoritative panels over the past 40 years that support this position including studies supported by USDA and CDC. Eliminating non-judicious antibiotic uses in food animals would help protect the American people against drug-resistant infections and extend the utility of existing antibiotics. This concludes reflects a broad consensus within the medical, scientific and public health communities. Such measures have been advocated repeatedly by the World Health Organization and the National Academy of Sciences, and as you have heard here today, have already been implemented across Europe.

IDSA is very encouraged by FDA's new draft guidance to industry which establishes a policy framework for judicious food animal antibiotic use. We view this new guidance as an important first step. Both FDA's guidance and PAMTA provide elements of the overall policy framework that Congress should consider as it moves forward to develop and enact legislation.

We are concerned, however, by FDA's apparent decision to rely on drug companies to voluntarily remove growth promotion and feed efficiency claims from their drugs' labels. Past experience suggests that this will take years or decades and many companies will not comply. Therefore, we urge Congress to expedite the process through legislation.

We also are concerned that FDA does not specify its plans for eliminating those uses of antibiotic in food animals for prevention, control and treatment that likewise may be non-judicious. These also must be addressed.

U.S. experts also require access to reliable and standardized data regarding the scope of antibiotic consumption in humans and animals. The lack of data in both the human health and agricultural settings impedes our ability to respond effectively to the antibiotic resistance problem. Although the U.S. Animal Drug User Fee Amendments, or ADUFA, legislation of 2008, as mentioned earlier, strengthened FDA's ability to collect animal antibiotic sales and distribution data. This was only for national-level data. What we need are local-level data reported by animal species. Of importance, also pharmacists do not control antibiotic distribution in the agricultural sector. Instead, feed mill operators are responsible for mixing animals into antibiotic feed and they control antibiotic distribution from the drug manufacturers to our Nation's farmers. Given feed mills' key role in distributing these lifesaving drugs, they must become better integrated into the infrastructure for protecting antibiotic by tracing and regularly reporting to the FDA the amount of antibiotics being consumed by each animal species.

In conclusion, the Subcommittee on Health has a long history of leadership in addressing our Nation's most pressing public health issues. Today, IDSA calls upon you to help protect our patients and the health of every American by adopting strong measures including PAMTA to end non-judicious antibiotic use in food animals and to require that other food animal uses of these precious drugs be supervised by a veterinarian within a valid veterinarian-client-patient relationship. We also urge the committee to move with haste to enact the Strategies to Address Antimicrobial Resistance, or STAR Act, which will significantly strengthen U.S. antibiotic resist-

ance efforts. Finally, we urge you to enact statutory incentives to spur new antibiotic development.

Thank you, and I will be happy to answer questions.

[The prepared statement of Dr. Johnson follows:]



Testimony of the Infectious Diseases Society of America (IDSA)

Antibiotic Resistance and the Use of Antibiotics in Animal Agriculture

Presented by James Johnson, MD, FIDSA, FACP

Before the House Committee on Energy and Commerce Subcommittee on Health

July 14, 2010

The Infectious Diseases Society of America's (IDSA) Statement on

Antibiotic Resistance: Promoting Judicious Use of Medically Important Antibiotics in Animal Agriculture

Before the House Committee on Energy and Commerce Subcommittee on Health

July 14, 2010

The Infectious Diseases Society of America (IDSA) appreciates this opportunity to speak in support of the House Energy and Commerce Committee Health Subcommittee's efforts to promote the appropriate ("judicious") use of medically important antibacterial drugs ("antibiotics") in animal agriculture. My name is James R. Johnson, MD, FIDSA, FACP. I am an infectious diseases specialist and a Professor of Medicine at the University of Minnesota School of Medicine. I also am a member of IDSA's Antimicrobial Resistance Work Group.

IDSA represents more than 9,000 physicians and scientists devoted to patient care, prevention, public health, education, and research in the area of infectious diseases. Our members care for patients of all ages with serious infections, including meningitis, pneumonia, tuberculosis (TB) and HIV/AIDS, emerging infections like the 2009 H1N1 influenza virus, food-borne diseases caused by *Salmonella*, *Campylobacter*, and *Escherichia coli* (*E. coli*), and diverse infections caused by antibiotic-resistant bacteria. Among the most concerning antibiotic-resistant organisms are methicillin-resistant *Staphylococcus aureus* (MRSA), *Enterococcus*, *E. coli*, *Salmonella*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* and *Acinetobacter baumannii*.

To better protect our patients and the general public against antibiotic-resistant bacterial infections, IDSA strongly supports efforts to eliminate all non-judicious uses of antibiotics in human medicine and animal agriculture (e.g., cattle, swine, and poultry production and aquaculture), including H.R. 1549, the Preservation of Antibiotics for Medical Treatment Act (PAMTA) and the Food and Drug Administration's (FDA's) recently announced public health approach to address antibiotic use in animal agriculture. IDSA also supports the elimination of non-judicious uses of antibiotics in plant agriculture. Antibiotics currently are used inappropriately on fruit and vegetables (e.g., use of gentamicin as a pesticide in apple orchards[1]). However, we have been asked to limit our comments today to animal agriculture.

In the animal agriculture context, the elimination of non-judicious uses will mean the end of antibiotic use for purposes of growth promotion, feed efficiency, and routine disease prevention. We also support requiring all remaining uses of antibiotics to be carried out under the supervision of a veterinarian and within the boundaries of a valid veterinarian-client-patient relationship. Finally, we urge Congress to enact legislation requiring the collection of antibiotic consumption data in the United States in a manner that parallels data collection advances achieved within the European Union.

Today, many of us in the United States take antibiotics for granted—we do not realize how fortunate we are to have them. Many of our parents, grandparents, and great-grandparents were not so lucky. Prior to the discovery of antibiotics, many injuries and illnesses became death

sentences as there was no way to treat the common infections that were often associated with them. Antibiotics often are referred to as "miracle drugs," because patients traditionally only needed to take them for a number of days for most infections to be cured.

The development of antibiotics to treat serious and life-threatening infections has indeed been one of the most notable medical achievements of the past century. However, there is growing concern among infectious diseases specialists that the effectiveness of antibiotics in treating infections is being increasingly compromised by the ever-growing presence of drug-resistant bacteria. Drug-resistant organisms are plaguing Americans, and others around the world, including otherwise healthy individuals, in the community and healthcare settings alike. Antibiotic resistance is a serious threat to public health, to patient care and safety, and to national security. Antibiotic-resistant infections are extremely difficult to treat and frequently recur. These infections often result in tremendous pain, suffering, and disfigurement in adults, children and infants, have caused millions of deaths worldwide, and have been estimated to cost the U.S. health care system between $21 billion and $34 billion annually.

Chairman Pallone, Ranking Member Shimkus, and Subcommittee members, at the same time that the numbers of drug-resistant infections are increasing, we have seen a steep decline in the number of new antibiotics in development. This Subcommittee has conducted a series of hearings to gain a better understanding of the many factors that are contributing to the current antibiotic resistance crisis. These hearings are critically important, and IDSA applauds your efforts. IDSA was pleased to testify before the Subcommittee on June 9, 2010 about antibiotic resistance and the dire antibiotic pipeline problem.[2] As you may recall, IDSA's testimony explored several key themes:

- Antibiotics are a vital resource and a precious gift from prior generations, and we have a moral obligation to ensure this resource is available for future generations.
- Safe and effective antibiotics are urgently needed to treat serious and life-threatening infections caused by a growing list of drug-resistant bacteria.
- As with other diminishing resources (energy, forests, clean water, etc.), Congress and the Administration must establish policy to nurture both the conservation and restoration of antibiotics through the development of innovative antibiotics and other relevant tools (e.g., rapid diagnostics, vaccines, and other biologicals).
- We must adopt, promote, and continue to refine effective strategies to prevent both the emergence and transmission of resistant organisms, which undercut the effectiveness of our current antibiotic arsenal. Transmission of resistant organisms can be prevented by good infection control practices, effective immunization policies, and (for food-borne organisms) hygienic food production, processing, distribution, and preparation. Emergence of drug-resistant bacteria can be reduced by ensuring that antibiotics are used judiciously in all settings. Antibiotic stewardship strategies are the best way to achieve this goal.

Our statement today will examine in greater detail this last principle and specifically the need to eliminate all non-judicious uses of antibiotics in animal agriculture and to ensure that all antibiotic uses in animals be carried out under the supervision of a veterinarian within a valid

veterinarian-client-patient relationship.[1] Considerable efforts have been taken in human medicine to eliminate non-judicious antibiotic use. As described in our prior testimony, antibiotic stewardship programs and practices are being established in health care settings across the country. Stewardship can take the form of restricting which antibiotics are included in the health facility formulary or requiring preauthorization to prescribe a specific therapy. Additional mechanisms can include antibiotic order forms, formal prospective audit and feedback, de-escalation of therapy based upon microbiological data of what specifically is causing an infection, and dose optimization. Educational efforts focused on appropriate uses have targeted both providers and patients. Of critical importance, antibiotics used in human medicine require a prescription. In contrast to human medicine, although animal agriculture uses of antibiotics also contribute significantly to the development of drug-resistant pathogens, only limited measures have been taken in this setting to eliminate non-judicious uses. Also, appropriate marketing and distribution safeguards have not been implemented in the agricultural setting as tons of antibiotics are purchased over-the-counter without a prescription each year for use in animal agriculture.

ANTIBIOTIC RESISTANCE: THE COSTS ARE GREAT

The U.S. Centers for Disease Control and Prevention (CDC) has described antibiotic resistance as "one of the world's most pressing health problems", because "the number of bacteria resistant to antibiotics has increased in the last decade [and] ... many bacterial infections are becoming resistant to the most commonly prescribed antibiotic treatments." The World Health Organization (WHO) has identified antibiotic resistance as "one of the three greatest threats to human health." Infectious diseases physicians agree. The costs due to antibiotic resistance, both in the numbers of lives lost or devastated and in economic terms, are exceedingly high.

Drug-resistant bacteria, such as MRSA and resistant enterococci and *E. coli*, affect many hospitalized patients, and resistant bacteria likewise are impacting a growing number of people in the community, including healthy athletes, parents, working people, and children. A 2007 study published in the *Journal of the American Medical Association*[3] demonstrates that annually in the U.S. more than 94,000 people are infected with invasive MRSA, and nearly 19,000 die from MRSA alone – which is more deaths than are caused by emphysema, HIV/AIDS, Parkinson's disease, and homicide. CDC reports that nearly 2 million health care-associated infections (HAIs) and 90,000 HAI-related deaths occur annually in the U.S.[4] Most of these infections and deaths involve antibiotic-resistant bacteria. A February 2010 study published in

[1] The Animal Medicinal Drug Use Clarification Act of 1994 (AMDUCA; Public Law 103-396) defines a valid veterinarian-client-patient relationship as one in which:

1. A veterinarian has assumed the responsibility for making medical judgments regarding the health of an animal and the need for medical treatment, and the client (the owner of the animal or other caretaker) has agreed to follow the instructions of the veterinarian;
2. There is sufficient knowledge of the animal by the veterinarian to initiate at least a general or preliminary diagnosis of the medical condition of the animal; and
3. The practicing veterinarian is readily available for follow-up in case of adverse reactions or failure of the regimen of therapy. Such a relationship can exist only when the veterinarian has recently seen and is personally acquainted with the keeping and care of the animal by virtue of examination of the animal, and/or by medically appropriate and timely visits to the premises where the animal are kept.

the *Archives of Internal Medicine* showed that two common types of HAI—sepsis and pneumonia—killed 48,000 people and increased health care costs by $8.1 billion in 2006 alone.[5]

The direct and indirect economic costs associated with antibiotic-resistant infections are also enormous in terms of dollars spent, length of hospital stay, and loss of productivity. A recent analysis of antibiotic-resistant infections at Chicago Cook County Hospital[6] , when extrapolated nationwide, indicated that annually in the U.S. antibiotic-resistant infections are responsible for more than $20 billion in excess health care costs, more than $35 billion in societal costs, and more than 8 million additional hospital days.[7]

ANTIBIOTICS ARE UNIQUE

In addition to their extremely high level of effectiveness and the value they provide to society, antibiotics are unique among medicines in one critically important way. Unlike other drugs, over time antibiotics lose their ability to treat the diseases for which they were developed—due to the ability of bacteria to develop resistance to the antibiotic. Therefore, in an effort to prolong antibiotics' effectiveness for as long as possible, infectious diseases physicians and professional societies urge that antibiotics be used appropriately and sparingly and seek ways to limit unnecessary use of these drugs.

A CLEAR LINK BETWEEN ANTIBIOTIC USE IN ANIMAL AGRICULTURE AND ANTIBIOTIC-RESISTANT INFECTIONS IN HUMANS

Physicians, health care professionals, and public health and food safety advocates are greatly concerned about non-judicious uses of antibiotics in animal agriculture. The relationship between antibiotic-resistant infections in humans and antibiotic use in animal agriculture is complex, but well-documented. A large and compelling body of scientific evidence demonstrates that antibiotic use in animal agriculture contributes to the emergence of resistant bacteria and their spread to humans. For example, it is well documented that fluoroquinolone use in poultry was a major source of fluoroquinolone-resistant *Campylobacter* infections in humans, leading to treatment failures and an increased risk of death. Likewise, cephalosporin and fluoroquinolone use in food animals has led to cephalosporin and fluoroquinolone-resistant *Salmonella* infections in humans, also with adverse health consequences. A livestock-associated strain of MRSA, which was first encountered in the Netherlands in 2003 and now accounts for one fifth of human MRSA infections there,[8] was recently found also in swine in Iowa, and Illinois.[9] This food animal-derived MRSA strain has caused various human infections, including hospital outbreaks; serious skin, wound, lung, and heart infections; and, in a dairy worker, necrotizing fasciitis – also known as flesh-eating bacterial infection.[10] Many of the antimicrobial-resistant *E. coli* strains that cause urinary tract and bloodstream infection in humans appear likely to derive from food animals, having become resistant on the farm.

The evidence of a cause-and-effect link between food animal antibiotic use and drug-resistant infections in humans is broad-ranging and derives from numerous epidemiological, molecular epidemiological, ecological, and experimental studies. The threat to humans due to antibiotic use in animal agriculture includes both acquisition of resistant pathogens by humans (whether from the food supply, direct contact with animals, or environmental sources) and transfer of

resistance genes from animal to human bacterial populations. A broad consensus exists among relevant experts that, based on the available evidence, it is reasonable and prudent to conclude that the use of antibiotics in animal agriculture poses an important threat to human health that warrants urgent action.

That antibiotic use in animal agriculture can give rise to resistance in humans has long been recognized by the infectious diseases and public health communities. A 1995 report by the Office of Technology Assessment[11] listed at least a dozen earlier expert committee reviews of the health effects of antibiotic use in animal husbandry, dating to the 1969 Swann Report, a report by the Joint Committee on the use of Antibiotics in Animal Husbandry and Veterinary Medicine, chaired by Professor M. M. Swann.

The Swann Report concluded:

> *"the administration of antibiotics to farm livestock, particularly at sub-therapeutic levels, poses certain hazards to human and animal health; in particular it has led to resistance in enteric* [food-borne] *bacteria of animal origin. This resistance was transmissible to other bacteria, and enteric bacteria were transferable from animals to man."*

The United Kingdom banned the use of penicillin and tetracycline for growth promotion in 1971.[12]

In a 2000 report from a new expert review panel,[13] the World Health Organization (WHO) stated:

> *"Another source of resistance lies in our food supply. Since the discovery of the growth-promoting and disease-fighting capabilities of antibiotics, farmers, fish-farmers and livestock producers have used antimicrobials in everything from apples to aquaculture. Currently, only half of all antibiotics produced are slated for human consumption. Ongoing and often low-level dosing for growth promotion and prophylaxis [disease prevention] inevitably results in the development of resistance in bacteria in or near livestock, and also heightens fears of new resistant strains between species.*
>
> *"Vancomycin-resistant Enterococcus faecium (VRE) is one particularly ominous example of a resistant bacterium appearing in animals that may have 'jumped' into more vulnerable segments of the human population. The emergence of VRE in food can be traced to the widespread use of avoparcin (the animal equivalent of the human antibiotic vancomycin) in livestock. Moreover, with livestock production increasing in developing countries, reliance on antimicrobials is likewise expanding – often without guidelines in those nations where antibiotics are sold without prescription.*
>
> *"Often bacteria that are harmless to livestock are fatal to humans. This is true of a number of outbreaks that have taken the medical community by surprise. One example occurred in Denmark in 1998, when strains of multi drug-resistant Salmonella typhimurium struck 25 people, killing two. Cultures confirmed that the organisms were resistant to seven different antibiotics. Epidemiologists eventually traced the micro-*

> *organism to pork and to the pig herd where it originated. In 1998, 5,000 people in the United States learned the hard way about antimicrobial resistance when they fell ill with multi drug-resistant campylobacteriosis caused by contaminated chicken. The same drugs that eventually failed them had also been used in the poultry that turned up on their plates."*

In 2002, the journal *Clinical Infectious Diseases* published a special supplement,[14] based on a two-year review by experts in human and veterinary medicine, public health, microbiology, biostatistics, and risk analysis of more than 500 scientific studies on the human health impacts of antibiotic use in agriculture, which concluded the "*[u]se of antimicrobials in food animals contributes to the growing problem of antimicrobial resistance in animal and human infection."*

In 2003, a National Academy of Sciences report[15] stated, "*Immediate action must be taken to preserve the effectiveness of available drugs by reducing the inappropriate use of antimicrobials in human and animal medicine.*" The authors recommended a ban on the use of antibiotics as growth promoters in animal agriculture if those antibiotics also are used in human medicine.

A December 2003 report[16] of the proceedings of an expert workshop on the Scientific Assessment of Non-Human Antimicrobial Usage and Antimicrobial Resistance, sponsored by the United Nations Food and Agriculture Organization, WHO, and the World Animal Health Organization concluded:

> *"There is clear evidence of adverse human health consequences due to resistant organisms resulting from non-human usage of antimicrobials. These consequences include infections that would not have otherwise occurred, increased frequency of treatment failures (in some cases death) and increased severity of infections, as documented for instance by fluoroquinolone resistant human Salmonella infections. Evidence shows that the amount and pattern of non-human usage of antimicrobials impact on the occurrence of resistant bacteria in animals and on food commodities and thereby human exposure to these resistant bacteria."*

In 2004, the U.S. Government Accountability Office issued a report[17] to Congress stating, *"Scientific evidence has shown that certain bacteria that are resistant to antibiotics are transferred from animals to humans through the consumption or handling of meat that contains antibiotic-resistant bacteria. Many studies have found that the use of antibiotics in animals poses significant risks for human health."*

A 2006 study[18] by a noted expert on aquaculture stated: "*The accelerated growth of aquaculture has resulted in developments detrimental to the environment and human health, such as the widespread and unrestricted use of prophylactic antibiotics in this industry. The use of a wide variety of antibiotics in large amounts, including antibiotics useful in human medicine, has resulted in the emergence of antibiotic-resistant bacteria in aquaculture environments, in the increase of antibiotic resistance in fish pathogens, and in the transfer of these resistance determinants to bacteria of land animals and to human pathogens. It appears that global efforts are needed to promote more judicious use of prophylactic antibiotics in aquaculture as*

accumulating evidence indicates that unrestricted use is detrimental to fish, terrestrial animals, and human health and the environment."

Finally, a 2009 report[19] by the WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance states, *"A large number of studies have shown that the use of antimicrobial agents in food animals favors antimicrobial resistance among non-typhoid Salmonella and Campylobacter; later, these can transmit to and cause infections in people. This can then result in failure of antimicrobial treatment in people with resistant infections."*

THE DANISH AND BROADER EUROPEAN EXPERIENCE

Denmark banned the prophylactic (i.e., routine disease prevention) use of antibiotics in animal agriculture; it halted the growth promotion use of antibiotics in broiler chickens and adult swine (finishers) in 1998 and in all swine in 2000. Today in Denmark, all uses of antibiotics in animal agriculture must be accompanied by a prescription in a valid veterinarian-client-patient relationship. In addition, farmers, veterinarians and pharmacies must report the use and sale of antibiotics, and farm inspections are conducted regularly. In 2006, the entire European Union banned non-therapeutic use of antibiotics in animal agriculture due to the threat to human health.

Contrary to claims made by some in the U.S. agricultural sector, experiences in Denmark and other parts of Europe have shown that reductions in antibiotic use do not lead to increased pathogen loads in animals or on carcasses, more food-borne illness in humans, greater total antibiotic use in animals, or impaired animal health or farm productivity. The WHO determined that Denmark's ban achieved its stated public health goal of reducing resistant organisms in food animals in order to prevent related human resistance from emerging.

The ban on growth promoters has been shown to be beneficial to both animal and human health. As one example of Danish and European actions, Danish scientists determined that the use of avoparcin as a growth promoter led to a strain of VRE in food animals. Vancomycin and avoparcin are related drugs, and vancomycin is important to combating serious antibiotic-resistant human infections. In Europe, this strain of VRE spread to humans through the food supply, particularly contaminated meat and poultry. Before the European ban on avoparcin use in animals, Europeans commonly carried VRE in their intestinal tract. Following the avoparcin and related bans, studies showed a drop in related resistance patterns in animals, as well as reductions in humans (both colonization and disease).

The WHO also found that the Danish ban reduced human health risk without significantly harming animal health or farmers' incomes.[20] In fact, Danish government and industry data show that livestock and poultry production has increased since the ban, while antibiotic resistance has declined in animal agriculture, in meat, and in healthy and infected humans (in the case of VRE, and with similar trends for *Campylobacter*). The growth promoter ban implemented throughout Europe in 2006 was followed in subsequent years by sustained decreases in food-borne illness in Europe.[21]

A 2004 Swiss study[22] analyzed prescription patterns for medicated feedstuffs in the Swiss canton of St. Gall to determine whether Switzerland's ban on antibiotics for growth promotion,

introduced in 1999, had caused an increase in the therapeutic use of antibiotics given orally to piglets and fattening pigs. The study found that the ban on growth promoters did not lead to an increase in therapeutic uses in swine.

In Denmark, the only detectable impact of the growth promoter ban in animal agriculture was a short-term effect among weaning-age pigs.[23] Specifically, while there was some reduction in weaner productivity and a small increase in weaner mortality associated with the ban, these effects lasted only one year. Weaner productivity is currently higher and mortality lower than before the growth promoter ban took effect.[24] Danish pork production has increased by 40 percent since the ban.

A July 2010 study,[25] conducted by notable experts in the field, led to the conclusion that:

> *"From 1992 to 2008, a reduction of greater than 50 percent in antimicrobial consumption per kilogram of pig produced was observed in Denmark. This change was associated with the implementation of policies to discontinue the use of antibiotics as antimicrobial growth promoters. During the same period, overall swine productivity improved markedly, which suggests that the change in antimicrobial consumption has not had a negative impact on long-term swine productivity."*

U.S. POLICY APPEARS TO BE MOVING IN THE RIGHT DIRECTION

IDSA is encouraged by the growing support within Congress for the PAMTA legislation, which would phase out the use of the seven classes of medically significant antibiotics that are currently approved for non-therapeutic use in animal agriculture. IDSA also views favorably FDA's new draft Guidance to Industry 209,[26] issued on June 28, which establishes a policy framework regarding the judicious use of medically important antibiotics in animal agriculture. We believe FDA's guidance is a step in the right direction. However, Congressional action is necessary to quickly and fully implement this new policy. Embedded within FDA's guidance are two key principles:

1. The use of antibiotics important in human medicine should be limited in food-producing animals to those uses that are considered necessary for assuring animal health; and

2. The use of antibiotics important in human medicine should be limited in food-producing animals to those uses that include veterinary oversight or consultation.

IDSA strongly supports banning the use of antibiotics for growth promotion and feed efficiency, and requiring that all remaining uses of these drugs be carried out under the supervision of a veterinarian and within the boundaries of a valid veterinarian-client-patient relationship—which would effectively end over-the-counter sales of thousands of tons of antibiotics annually. The sale of antibiotics for use in human medicine requires a prescription; there is no sound reason to permit a lower standard for agricultural purposes, where considerably more antibiotics are used, and in much larger numbers of recipients. We also support clearly defining the limited instances in which antibiotics may be used judiciously in animal agriculture for purposes of disease prevention, as well as more closely monitoring, through enhanced data collection, all remaining

uses (targeted disease prevention, control, and treatment) to prevent non-judicious use. Implementing these changes will better protect our patients and the U.S. public against resistant infections and will help preserve the curative power of existing antibiotics. Both PAMTA and the principles articulated in FDA's new guidance offer elements of the complete framework Congress should consider as it moves forward to develop and enact legislation.

A concern with the FDA's guidance is the agency's apparent decision to rely on drug companies to voluntarily agree to remove growth promotion and feed efficiency claims from their drug labeling. Based on past experience, we believe this process will take years, if not decades, and that many companies are unlikely to comply. Therefore, we urge Congress to expedite this process by eliminating these uses through legislation.

We are concerned that FDA's guidance does not provide sufficient detail about how it plans to address non-judicious uses of antibiotics of importance to human medicine related to disease prevention and therapeutic uses. Therefore, in addition to limiting the marketing status of these drugs to prescription only, we believe FDA and Congress must work together to:

- Establish specific indications for antibiotic use and narrowly limit off-label uses of new and existing antibiotics;
- Define procedures for antibiotic administration that will expose only those animals that have a current need;
- Expand post-approval surveillance under the National Antimicrobial Resistance Monitoring System (NARMS)[ii] to include all drugs of importance to human medicine.

As drafted, FDA's guidance will permit consultation with a veterinarian rather than the veterinarian's direct oversight of the treated animal before an antibiotic can be prescribed. Obviously, FDA took into account logistical issues (the vast rural expanses and limited number of veterinarians within the U.S.) when it considered this principle. However, the consultation allowance, if included in FDA's final guidance/regulation, provides opportunity for abuse as it does not require a veterinarian's direct oversight of the treated animal within the context of a valid veterinarian-client-patient relationship as defined by AMDUCA. Accordingly, legislation or regulation, depending on which option is chosen, must be carefully crafted.

IDSA also urges a reassessment of existing FDA Guidance #152, which is the framework by which the agency approves new antibiotic products for use in animals. FDA must reevaluate the current ranking of drugs according to their importance to human medicine. In particular, the

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[ii] NARMS was established in 1996 as a collaborative effort between FDA's Center for Veterinary Medicine (CVM), U.S. Department of Agriculture (USDA), and the Centers for Disease Control and Prevention (CDC). NARMS monitors changes in antibiotic susceptibilities of selected enteric bacterial organisms in humans, animals, and retail meats to a panel of antibiotics important in human and animal medicine. Animal specimens for NARMS are collected from federally inspected slaughter and processing facilities, from healthy animals on farms, and from Veterinary Diagnostic Laboratories, including USDA's National Veterinary Services Laboratories. Animal and human isolates currently monitored in NARMS are non-typhoid *Salmonella*, *Campylobacter*, *E. coli*, and Enterococci. CDC also tests additional human isolates including *Salmonella* typhi, *Listeria* and *Shigella*. Retail meats collected from grocery stores were recently added to NARMS sampling. Accessed online at: http://www.fda.gov/AnimalVeterinary/SafetyHealth/AntimicrobialResistance/NationalAntimicrobialResistanceMonitoringSystem/default.htm.

agency should reconsider the criteria used to categorize antibiotics as "critically important" and "highly important" to human health. For example, IDSA believes fourth-generation cephalosporins should be considered "critically important," the same ranking currently given to third-generation cephalosporins. Third- and fourth generation cephalosporins are used to treat complicated, high-severity intra-abdominal infections, as well as invasive *Salmonella* infections in humans. WHO agrees with the categorization of fourth-generation cephalosporins as critically important.[27] We also support broadening the scope of Guidance 152 criteria beyond enteric pathogens. The current focus on enteric-only pathogens fails to consider the human risk posed by horizontal gene transfer or clonal spread of resistant strains of bacteria, including such species as *Enterococcus* and *E. coli*, which are intestinal commensals in food animals but extraintestinal pathogens in humans.

Additional investments into new vaccines for animals that would prevent infections and result in decreased antibiotic use in animals, as well as rapid diagnostics to more quickly identify bacterial infections, also would be helpful. These new tools would help to prevent the emergence and transmission of infections and help to protect both animal and human health.

ELIMINATING NON-JUDICIOUS USES WILL NOT HARM U.S. FARMERS

IDSA recognizes that eliminating non-judicious uses of antibiotics in animals will require changes in the agriculture industry's current practices. Ultimately, protection of the public's health must be our highest priority, and we believe terminating these uses can be accomplished in a way that minimizes costs to the agricultural sector. As previously noted, studies have shown that food animal producers in Denmark have adapted to such policy shifts without disruption to farm productivity or a negative impact on animal health.

In addition, a USDA analysis of U.S. finishing pigs found that, "*farms that use non-therapeutic antibiotics have costs of production that differed little from those that do not. Any productivity improvement from use of antibiotics has not been large enough to offset the additional expenses, suggesting the viability of alternative practices or technologies to reduce disease or improve feed efficiency at finishing stages.*"[28] For U.S. poultry producers, the benefits of non-therapeutic antibiotics have been shown to be very limited and less than the cost of the drugs.[29]

U.S. ANTIBIOTIC CONSUMPTION AND RESISTANCE DATA COLLECTION MUST BE STRENGTHENED

To control the antibiotic resistance epidemic, U.S. experts (government and non-government) need ongoing access to reliable, standardized data regarding the scope of antibiotic consumption in humans and animals. "Consumption" data includes drug use data (i.e., prescribing data) as well as manufacturers' distribution and sales data. The lack of adequate U.S. antibiotic consumption data impedes our understanding of geographic and temporal trends in antibiotic resistance. Greater understanding of these factors will contribute to more effective and targeted interventions to reduce unnecessary antibiotic use and resistant infections. These include: 1) targeting appropriate antibiotic use interventions to the geographic areas and drugs of greatest importance, and 2) predicting and responding to new resistance problems based on changes in antibiotic utilization.

In the agricultural context, the collection of accurate antibiotic consumption data will make information currently collected under the NARMS program of greater relevance, because it could be used to show possible correlations between antibiotic use and the development of resistance. The United States is far behind other countries in collecting, and benefiting from, antibiotic consumption data. The Danish Integrated Antimicrobial Resistance Monitoring and Research Program (DANMAP) performs continuous monitoring of both consumption data and resistance data in humans, animals, and food. Human consumption data is collected from the pharmaceutical industry and the Danish Medicines Agency, while DANMAP's "VetStat" system collects food animal data by species from pharmacies, farms, feed mills, and veterinary practitioners. On a Europe-wide level, the European Surveillance of Antimicrobial Consumption (ESAC) system collects human and more limited animal consumption data from 34 countries, while the European Antimicrobial Resistance Surveillance System (EARSS) collects resistance data. The inputs are largely standardized since countries must adhere to WHO standards regarding measurement ("defined daily doses") and classification of antibiotics.

Better understanding of the correlation between antibiotic consumption and the development of resistance holds potential benefits for U.S. public health efforts. In the earlier example of the avoparcin ban in Europe, it was the DANMAP and other surveillance efforts that helped the Danes and other Europeans see the benefit that elimination of avoparcin as a growth promoter in animal agriculture had on the reduction of VRE in humans.

The U.S. Animal Drug User Fee Amendments (ADUFA; Public Law 110-316) enacted in 2008 contained a provision to begin to strengthen FDA's authority to collect animal antibiotic sales and distribution data from the manufacturer by requiring data based on a calendar year, as opposed to the anniversary date of the product's approval. However, the ADUFA data do not include retail-level use data and are at the national level only. To really understand how antibiotics are being used on U.S. farms, the ADUFA requirements must be strengthened to mandate collection of antibiotic use data at the local level as well. Consumption data also must be collected by species (swine, chicken, turkey, cattle) and in a unit of measure that can be compared across species and localities. European countries collect such data at the farm and feed mill level; so should the United States. Collection of such data, along with strengthened surveillance, will enable us to understand how and where antibiotics are being used, including non-judiciously. The urgency for better data will not be reduced once the FDA's new principles for growth promotion and veterinary supervision of antibiotics become operational. To the contrary, comparable and reliable data will become even more important as a way to monitor whether the agricultural sector (e.g., farms, feed mills, and others) are complying with these new principles.

While IDSA supports further strengthening the ADUFA data collection provisions, we also believe there are steps that federal agencies can take under current authority to assist in surveillance and monitoring of antibiotic use in animal agriculture. The U.S. Department of Agriculture (USDA) could use the National Animal Health Monitoring and Surveillance System to monitor trends in the volume and type of antibiotics used in animal agriculture by adding targeted questions that would help determine the total volume and type of animal antibiotics used. They also could enhance the Agricultural Resource Management Survey to include

information about the volume and efficiency of antibiotic usage to help producers make better decisions about optimal use of antibiotics and to allow public health officials a better understanding of a potential source of resistance. Additionally, NARMS could be expanded to gather information about additional pathogens to provide public health officials a wider array of information to determine the magnitude of the antibiotic resistance problem.

IMPACT STATEMENT AND MANAGEMENT PLAN

IDSA supports requiring manufacturers of new antibiotics intended for use in animal agriculture to first evaluate the potential impact that approval of the drug would have on the development of antibiotic resistance and, subsequently, to develop a management plan to limit potential antibiotic resistance from occurring. New drug sponsors also should be required to submit updates to the impact statement and management plan within three years after the initial approval of the antibiotic.

These impact statements and management plans should be made public so that researchers can use each to study and strengthen our understanding of the science of predicting, preventing, and controlling resistance development. However, IDSA believes that neither the impact statement nor the management plan should be used for enforcement purposes.

CONCLUSION

The problem of antibiotic resistance is complex and multi-factorial. In contrast to efforts by the medical community to begin to curtail human overuse and misuse of antibiotics, the U.S. is among the last developed countries to implement similar control polices for antibiotic use in animal agriculture. It is inescapable that non-judicious uses of antibiotics in animals' feed and water over prolonged periods for purposes of growth promotion, increased feed efficiency, and routine disease prevention contribute to antibiotic resistance and create health dangers for humans.

No single strategy can solve the antibiotic resistance problem—a multi-pronged approach is required. We must promote the development of new priority antibiotics to treat serious and life-threatening infections. We must prevent the emergence and transmission of resistant infections through research into new vaccines and diagnostics and implementation of other effective infection prevention and control initiatives. And we must eliminate all non-judicious uses of antibiotics, in human medicine and animal agriculture alike.

The Subcommittee on Health has a long history of leadership in addressing our nation's most pressing public health issues. Today, we call on you to adopt strong measures to end non-judicious uses of antibiotics in animal agriculture and to require that all other uses of these drugs in animals be carried out under the supervision of a veterinarian and within the boundaries of a valid veterinarian-client-patient relationship. Such measures have been advocated repeatedly by the World Health Organization, the National Academy of Sciences, and many medical and public health organizations, and successfully implemented by multiple European nations in the past one to two decades. We also urge the Committee to move with haste to enact PAMTA, as well as the Strategies to Address Antimicrobial Resistance Act (H.R. 2400), which we believe

will significantly strengthen U.S. antibiotic resistance data collection, surveillance, research, and prevention and control efforts.

Any new policy on antibiotic use in animal agriculture should be mandatory, retroactive to already-approved drugs, and enforceable. This will help reduce antibiotic resistance in order to save lives and protect public health.

Thank you again for the opportunity to testify on this important issue. IDSA stands ready to assist the Subcommittee in any way that we can.

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Mr. PALLONE. Thank you, Dr. Johnson.
Dr. Hansen.

STATEMENT OF GAIL R. HANSEN

Dr. HANSEN. Chairman Pallone and Ranking Member Shimkus and members of the subcommittee, good afternoon, late afternoon, and thank you for inviting me. I am Gail Hansen. I am a veterinarian. I am a member of the AVMA, the American Veterinary Medical Association, and I also a Senior Officer with the Pew Charitable Trust.

Obviously, I care very deeply about this issue and I have worked on antimicrobial resistance from a lot of different angles. I was a State public health veterinarian for the Kansas Department of Health and Environment in Kansas, obviously, in working with both human and animal diseases. I was also a veterinarian in private practice for several years in Washington, New York City, North Carolina, and before I even got into veterinary school I was interested in this topic because I worked for the Food and Drug Administration, what was then the Bureau of Veterinary Medicine, in 1978. That was the year that FDA first proposed eliminating some drugs as growth promoters in animal feeds based on the science, and we are still here today.

I want to pick out one experience with a bacteria called Campylobacter that you have heard about to illustrate the real problem of antibiotic resistance, and let me give you a quick background on Campylobacter. It is a real common foodborne disease similar to Salmonella and E. coli, which you may be familiar with. You get the same sort of symptoms. You have diarrhea, you have vomiting. It is pretty unpleasant. There can be some nasty complications that can occur with Campylobacter. I guess the good news about that is that we can treat it with antibiotic. The bad news is that the bacteria is becoming resistant to antibiotics. We also that this is a bacteria that is found in poultry and cattle. People get it from eating contaminated poultry or meat, as we have heard before.

So let me talk to you about the Campylobacter outbreak that I dealt with in Kansas in 1998 in Salina, Kansas. We had a middle school where we had over 100 people that got sick with Campylobacter. The physicians were using Cipro and tetracycline to treat people because those are the drugs that all the books said you should use, but then we found out that Campylobacter, that Campylobacter was resistant to both of those drugs so the physicians couldn't use those drugs. There was unequivocal evidence that the resistance came from antibiotic that were given to animals. Tetracycline was used and still is used in cattle and poultry, and at that time Cipro was used in poultry and it is still used in cattle today.

So antibiotic resistance from feeding low levels of antibiotics to animals is real. It is here. We have got 40 years of science-based evidence and it is very clear. I have a book here which I have given you an annotated version of the bibliography of this that has some of the peer-reviewed studies that we have over the last 40 years, so there is plenty of science.

Antibiotics are overused in farm animals, in industry farming to the detriment of human health. Animals are fed low levels of antibiotics for growth promotion in the absence of disease, and especially when bacteria come in contact with low levels of antibiotics, it makes it much easier for them to become resistant to antibiotic. That whole thing of what doesn't kill you makes you stronger works for the bacteria as well. And then that resistance gets transferred to people and ultimately the antibiotics that we use for people don't work anymore for people and they don't work for animals either, and that is pretty scary.

But there are some effective alternatives to low-level antibiotic use available to farmers and ranchers. Just this last Saturday, I got back from a trip to Denmark looking at what Dr. Henriksen talked about, and how their industrial farmers are able to efficiently raise pork without the use of non-therapeutic antibiotics. Farmers only give antibiotics, as he said, when they are prescribed by a veterinarian for a specific disease. The farmers at that point worked with veterinarians and with others to find effective management strategies that work.

So the American public really needs Congress to pass PAMTA. The FDA guidance document is not likely to fix the problem by itself. We need your help, and that is what PAMTA does. PAMTA disallows the use of seven classes of antibiotics that are critically important for human health to be used for non-therapeutic purposes unless it can be shown that the use doesn't contribute to antibiotic resistance in people. It still allows antibiotics to be used to treat sick animals. We absolutely have to have that. But we want to make sure that we protect antibiotics for people and animals. We can help the farmers and ranchers get past this outdated and very dangerous practice of feeding antibiotics to healthy animals.

Unfortunately, the American Veterinary Medical Association's position on PAMTA is different from mine and from many other veterinarians. I am disappointed, I guess is the best word, that the AVMA has not yet come to the same conclusions that the American Medical Association and the American Nurses Association, the American Academy of Pediatrics has come to on the importance of this bill.

Thank you for the opportunity to testify. I would be happy to answer any questions.

[The prepared statement of Dr. Hansen follows:]

Testimony before the

House Committee on Energy and Commerce, Subcommittee on Health

July 14, 2010

Gail R. Hansen, D.V.M., M.P.H.
Senior Officer, Human Health and Industrial Farming Campaign
The Pew Charitable Trusts

Good afternoon Chairman Pallone, Chairman Waxman, Chairman Emeritus Dingell, Ranking Member Shimkus and members of the Health Subcommittee. My name is Gail Hansen and I am a Senior Officer with The Pew Charitable Trusts. I appreciate the opportunity to speak before you today about the routine use of antibiotics in food animal production.

I am a veterinarian who cares deeply about animal and human health and welfare. I have spent most of my professional career working to keep animals and people healthy. For 12 years, I was in private clinical practice, mostly in companion animals. For another 15 years I served in local and state public health departments; 12 years as the State Public Health Veterinarian and three as the top Kansas State Epidemiologist. In Kansas I was responsible for creating and implementing policy, for coordinating disease tracking and conducting outbreak investigation for all infectious diseases in the state. In addition, I served on the executive board of the National Association of State Public Health Veterinarians (NASPHV) for eight years and was the Infectious Disease Chair for the Council of State and Territorial Epidemiologists in 2007. I am a member of the American Veterinary Medical Association (AVMA) and was a U.S. Congressional Fellow for the AVMA from 2008-2009.

My message to you today is simple:

1) Antibiotics are overused in industrial farming to the detriment of human health. Antibiotic overuse has spurred generations of bacteria that are causing life threatening illnesses that were once easily treatable with antibiotics.
2) Effective alternatives are available to agribusiness. This has been demonstrated by practices adopted abroad, as well as in the United States.

3) Congress has the opportunity to enact legislation that will curtail the use of antibiotics in industrial food animal production without having significant economic impact on the industry.

The health risks posed by antibiotic use in industrial farming: Industrial farming routinely and extensively incorporates low dose concentrations of antibiotics in the feed and water of healthy food animals for growth promotion, feed efficiency and other uses where the animal has not been exposed to disease. A wide range of antibiotics, such as penicillin and tetracycline, are available over the counter for use in food animal production in this country[1]. The United States Food and Drug Administration (FDA) allows this practice under its current rules and regulations and yet almost none of the over the counter uses have been reviewed by the FDA to ensure they are safe with respect to antibiotic resistance.

FDA approved over-the-counter antibiotic sales more than 50 years ago when our understanding of the mechanics and implications of antibiotic resistance was still in its infancy and the largest safety concern was drug residues in meat. The seven classes of antibiotics—lincosamides, sulfonamides, tetracylcines, aminoglycosides, macrolides, penicillin and streptogramins—deemed critically important for human use were never reviewed by FDA for implications to human health caused by antibiotic resistance. Today, the science of antibiotic resistance is more advanced and well-understood. The guidelines for **new** antibiotic approval and withdrawal have been updated to require resistance-related safety demonstration. However, the agency has said that it is extremely difficult for it to reevaluate previously approved drugs based on updated criteria.

In 1977, when FDA attempted to take steps to curtail antibiotic use, the agency's efforts were thwarted by Congress.[2] Even the recommendations of the nation's leading research institutions were ignored.[3]

In the 1980s, the National Research Council and Institute of Medicine warned of the dangers of overuse of antibiotics in food animals.[4] In 2003 the National Academy of Sciences, which were

created by Abraham Lincoln in 1863 to serve as scientific advisors to Congress, stated: "Clearly, a decrease in the inappropriate use of antimicrobials in human medicine alone is not enough. Substantial efforts must be made to decrease inappropriate overuse of antimicrobials in animals and agriculture as well." [5]

These findings are of little surprise to those of us who have studied medicine. Every introductory microbiology class teaches that using antibiotics at levels that are below a therapeutic dose sets up a perfect environment for bacteria to develop resistance. We now know that resistance to antibiotics can develop rapidly, extend to other antibiotics in the same or different class and be shared among bacteria in a variety of ways; up to 95 percent of antibiotic resistance is from sharing genetic material for resistance[6].

Four decades of rigorous science and research confirm that the routine use of antibiotics in food animal production promotes the development of dangerous drug-resistant bacteria that can spread to humans. The notebook in front of me today contains 40 years of independent, peer-reviewed studies demonstrating this scientific link. I am submitting with my written testimony today an annotated bibliography summarizing this research.

Within this scientific literature one of the most compelling stories concerns Cipro®. Cipro® is an antibiotic that belongs to a class of drugs called fluoroquinolones and was a key antibiotic used to treat members of Congress and staff after the anthrax attack in October 2001. In Australia, where fluoroquinolones have never been approved for use in food animal production, domestically acquired human infections with Cipro®-resistant Campylobacter are still either absent or rare[7]. This is in stark contrast to the situation in the U.S., where fluoroquinolone use in poultry was common from 1995 to 2005. There was controversy within the veterinary community about whether it should be allowed in poultry water due to the concerns that it would lead to antibiotic resistance in humans. FDA monitored resistance and saw that resistance to Cipro® in human illnesses was increasing at a rapid rate: from 12.9 percent in 1997 to 21.7 percent in 2005.[8] In comparison, Cipro®-resistant Campylobacter rates in the U.S. had held steady at about 1 percent for the 10 years it was used exclusively in human medicine. In response, FDA began the process to remove fluoroquinolones from routine use in poultry in

2000. The drug class was banned from routine poultry use in 2005 after protracted legal challenges.

Use of the antibiotic known as Avoparcin is another good example. Avoparcin is a drug that was widely used in Europe for growth promotion in animals, but not used in people. However, it was found to share resistance with a very closely related to and critically important human drug, vancomycin. Vancomycin is a powerful drug and is used only after treatment with other antibiotics has failed. In the countries where avoparcin was fed to livestock, animals had intestinal bacteria resistant to vancomycin as well. In the countries that didn't use avoparcin, including the U.S. and Sweden, livestock did **not** have intestinal bacteria resistant to vancomycin. When avoparcin use was banned in Denmark, a World Health Organization (WHO) report found that "the termination of [avoparcin] in Denmark has dramatically reduced the food animal reservoir of enterococci resistant to these growth promoters, and therefore reduced a reservoir of genetic determinants (resistance genes) that encode antimicrobial resistance to several clinically important antimicrobial agents in humans."[9] In English, this simply means that banning the use of avoparcin as a growth promoter has significantly reduced the number of antibiotic resistant bacteria.

There are additional examples of such links between antibiotic use in livestock and poultry and human cases of antibiotic resistance. For example, Dr. James Johnson, testifying today, is a prominent expert in the field of study connecting resistant urinary tract infections in women to resistant *E. coli* in food animals.[10]

There are proven alternatives for many uses of antibiotics in industrial farming: In contrast to the clear impacts on human health, the rationale for much of the antibiotic use in industrial farming is tenuous.

First, using antibiotics for growth promotion is an outdated practice and yields questionable benefits to farmers in modern agriculture. In U.S. studies, little or no benefits were seen with nontherapeutic antibiotic use in poultry.[11] A United States Department of Agriculture study found that in growing and finishing pigs, those that are 6 weeks to 5 months old, the benefits of

using nontherapeutic antibiotics are so small that either none were found[12] or that they were insufficient to offset the expense of the antibiotics themselves.[13] In Denmark, experts presumed that antibiotics produced a 10 percent feed efficiency advantage, based on data from the 1950s, but in modern agriculture, more recent studies have found almost no effect on feed efficiency.[14] Even so, enormous numbers of animals are fed the drugs. By way of example, one drug company supplies antibiotics in feed for 632 million chickens per year.[15]

Second, it is not necessary, as some claim, to dispense antibiotics on a massive scale to protect food safety. On the contrary, rarely has food safety been shown to be adversely affected by decreasing the amount of nontherapeutic antibiotics given to food animals. In fact, in the U.S., there were significant reductions in the types of foodborne illness normally acquired from eating chicken between 1995 and 2000, the same period that the poultry industry reduced antibiotic use.[16] Denmark data shows removal of in-feed antibiotics similarly had no negative impact on food safety.[17] FDA Principal Deputy Commissioner Dr. Joshua Sharfstein confirmed in his House Rules Committee testimony last year, "Eliminating these [growth promotion and feed efficiency] uses will not compromise the safety of food."[18]

This is not to say that antibiotics have no place in food animal production. As a veterinarian, I know that appropriate antibiotic use – to treat sick animals or prevent the spread of infection in animals at heightened risk – can be beneficial to animal and human health. But just as surely, inappropriate uses, where there is no disease present, are contrary to human health practices. Many other public health veterinarians and farmers agree with these principles and some have asked that I submit statements on their behalf with my written testimony.

It also is clear that antibiotics for animal use should be kept to the same standards used in human medicine. Bacterial resistance does not have a different effect on humans and animals. Resistance can transfer between species of bacteria. Antibiotics should be prescribed only to treat individuals and groups of animals exposed to disease. Over the counter use of antibiotics is not allowed in human medicine or for our pet dogs and cats and should not be allowed in food animal production.

The World Animal Health Organization (OIE), the Food and Agricultural Organization of the United Nations (FAO) and the WHO recognize that the animal and human health sectors have a shared responsibility to minimize antibiotic resistance.[19] And as all three have jointly stated, antimicrobial usage, if necessary, should always be a part of, not a replacement for, an integrated animal health program.[20] The routine use of antibiotics should never be a substitute for good animal health management and the routine use of antimicrobials in control programs should be regularly assessed for effectiveness and necessity.

Efforts to prevent disease and maintain animal health and welfare should continuously be in place to reduce the need for routinely administered antibiotics.[21] In other words, hygiene, disinfection, bio-security measures, nutrition, cleaning practices, enhanced animal observation, changes in how much time a pen stays open after it has been cleaned, animal density, vaccinations and environmental changes all should be considered before antibiotics are administered. Veterinarians, together with farmers and ranchers, should be jointly responsible for the health of animals on a farm. It is not enough that veterinarians be involved with the mixing of antibiotics at the feed mill or at production company headquarters; they must regularly visit the animals and establish a proper veterinary-client-patient relationship. To help increase the number of large animal veterinarians available to do such work, Congress could consider legislation to incentivize entry into this field.

The search for solutions: As a veterinarian, when I look at antibiotic use in food animal production, I am dismayed. It is clear to me that the industry has become too reliant on antibiotics. Today, these life-saving drugs can mask poor animal husbandry practices that lead to diseases that otherwise might not occur. An animal production system that requires regular antibiotic inputs to keep the animals from becoming sick is a flawed system. We have long recognized that routine use of antibiotics in humans leads to antibiotic resistance. We do not try to prevent outbreaks of human diseases using population scale antibiotic treatment except in extremely rare circumstances. Instead, we control infections using vaccination, hygiene and other public health interventions. Yet, we have largely ignored these principles in modern food animal

production and enabled a system that relies too heavily on antibiotics to do what good animal husbandry could accomplish without putting human health at risk.

Mr. Chairman, the Pew Campaign on Human Health and Industrial Farming was founded on the recommendations of a blue ribbon commission that cited the routine, non-therapeutic use of antibiotics on industrial farms as the number one public health problem created by these large operations. The Pew Commission on Industrial Farm Animal Production acknowledged that food animals will need to be produced in large-scale operations in order to feed Americans and others in the world as well as compete in the global marketplace. But it stated the current system utilizing routine low levels of antibiotics presented an unacceptable level of threat to public health and damage to the environment.

To that end, I have just returned from a week-long fact-finding mission to Denmark to discover how they managed to successfully ban the nontherapeutic use of antibiotics in food producing animals in an industrial farm setting. Denmark is one of the world's largest exporters of pork. Danish food animal production is industrialized and highly intensive.

Recognizing the potential for a health crisis, Denmark stopped the administration of antibiotics used for growth promotion in broiler chickens and adult swine (finishers) in 1998 and in young swine in 1999. Today in Denmark, all uses of antibiotics in food animal production must be accompanied by a prescription in a valid veterinarian-client-patient relationship and veterinarians cannot profit from the sale of antibiotics. In addition, farmers, veterinarians and pharmacies must report the use and sale of antibiotics. Although the U.S. food animal production and animal drug industries often claim that the ban was costly and ineffective, the World Health Organization found that the Danish ban reduced human health risk without significantly harming animal health or farmers' incomes.[22] In fact, Danish government and industry data show that livestock and poultry production has increased since the ban, while antibiotic resistance has declined on farms and in meat.[23]

I saw first-hand how Denmark has learned to successfully raise animals using antibiotics only when prescribed by a veterinarian. On my trip, I had a chance to visit an industrial swine farm and interview the farmer and his veterinarian, tour the largest slaughter facility in Denmark,

discuss genetic improvements in swine and talk to a veterinarian from the Ministry of Food, Agriculture and Fisheries about the government's antibiotic use tracking system. I also had an opportunity to hear what researchers at both the Danish Technical University and the non-government affiliated Pig Research Center are doing on behalf of farmers. They focus on maximizing meat production without using nontherapeutic antibiotics, while continuing to improve the welfare of the animals and meet strict regulations within Denmark and the European Union. The trip was very informative and everyone was very forthcoming. The people I met extended an open invitation to any group that would like to learn for themselves what Denmark has done, what has worked, what has not worked and what they see as the future of Danish food animal production.

In human medicine there are several successful programs in this country that promote the wise use of antibiotics; plus antibiotics are available by prescription only. For example, CDC's educational campaign, "Get Smart: Know When Antibiotics Work," teaches both the provider and the patient when and how antibiotics should be used. Data from the CDC's *National Ambulatory Medical Care Survey* confirm the campaign's impact on reducing antibiotic use for acute respiratory tract infections among both children and adults. The survey showed a 20 percent decrease in prescribing for upper respiratory infections and a 13 percent decrease in prescribing overall for all office visits.[24]

As Dr. Sharfstein's testimony today noted, FDA just last month acknowledged the problem of overuse of antibiotics in industrial farming as an urgent public health issue. Over the past 30 years, FDA has sporadically proposed methods to curtail the overuse of life-saving antibiotics in food animal production. And for more than 30 years, opponents have managed to block progress, while antibiotics become less and less effective in saving lives. The newly released FDA draft guidelines for antibiotic use correctly calls for eliminating the use of antibiotics for growth promotion and feed efficiency, which the FDA deems non-judicious. The agency's call for "judicious" use in preventing sickness suggests several principles for evaluating the appropriateness of such uses.[25]

While the draft guidelines are a welcome first step, agribusiness could continue to feed antibiotics to entire flocks or herds to prevent illnesses they may never encounter. This approach to prevention is not allowed in human medicine and it should not be allowed in animals. The draft guidelines are only voluntary and the agency has not indicated its plans to proceed with enforceable requirements. FDA must develop effective, mandatory solutions to the threat of antibiotic resistance to human and animal health. The Pew Charitable Trusts is joined by the leading health and medical organizations in this country in asking the agency to move expeditiously toward the issuance of regulations that will control the widespread use of antibiotics on industrial farms. Unfortunately, regulatory action has been a slow and arduous process, particularly in an atmosphere of industry resistance.

In the meantime, Congress must not wait for FDA. Lawmakers should take swift action to pass the Preservation of Antibiotics for Medical Treatment Act (PAMTA, H.R. 1549). This legislation would disallow the routine use of seven classes of antibiotics vitally important to human health in food animal production unless animals or herds have been exposed to disease or unless drug companies can show with reasonable certainty that their use does not harm human health through antibiotic resistance.

PAMTA would continue to allow the use of antibiotics not deemed critically important for human use to be sold over the counter to farmers and ranchers as needed. This means drugs such as ionophores could still be used in food animal production, because they are not related to drugs used in human medicine and at this point, we believe, do not pose a risk to human health from antibiotic resistance. PAMTA would **not** bar the use of antibiotics for treatment of sick animals.

There is general agreement that antibiotics have a place in animal production. PAMTA does not challenge that notion. The bill would still allow veterinarians to prescribe antibiotics to treat disease while minimizing the reservoir of antibiotic resistant bacteria. This is a solution that works well for human and animal health.

As a member of the American Veterinary Medical Association (AVMA), I am disappointed in the stance that AVMA has taken to oppose PAMTA. Ironically, PAMTA is a pro-veterinarian

bill designed to restore the veterinary-client-patient relationship between food animals and medical care. There are many veterinarians in the AVMA who do not share the official viewpoint of the AVMA on PAMTA. The leading medical and public health organizations in the U.S. including the American Medical Association, American Academy of Pediatrics, American Nurses Association and the Infectious Diseases Society of America have all independently called for strictly limiting antibiotic resistance by curbing the amount of drugs fed to food animals. In addition, these groups all endorse PAMTA.

The U.S. has a long, proud history of helping farmers and ranchers and maintaining our top place in the global food market. It is clear that antimicrobial resistance from our overuse of antibiotics in food animals has reached a crisis point. My experience in Kansas and my animal and human health expertise lead me to be confident that American farmers and ranchers along with our best scientists can find solutions. Congress can take a big step toward reducing overuse and protecting life-saving antibiotics by moving forward with PAMTA. Every day that we delay implementing effective and unambiguous legislation to curtail the overuse of antibiotics in food animal production, the risks to the American people increase.

Thank you for the opportunity to testify on this very important issue. I am happy to answer any questions you may have.

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Antibiotic Resistance and Food Animal Production: a Bibliography of Scientific Studies (1969-2010)

This bibliography lists the latest published scientific and economic literature concerning the contribution of routine antibiotic use in food animals to the growing public health crisis of human antibiotic resistance. Research on how antibiotic use in food animal production contributes to the growing health crisis of antibiotic resistance dates back more than 30 years. As Dr. Frederick J. Angulo, Acting Associate Director of Science in CDC's National Center for Environmental Health and the Agency for Toxic Substances and Disease, said in a August 1, 2009, news article in the *Journal of the American Veterinary Medical Association*:

> "There is scientific consensus that antibiotic use in food animals contributes to resistance in humans. And there's increasing evidence that such resistance results in adverse human health consequences at the population level. Antibiotics are a finite and precious resource, and we need to promote prudent and judicious antibiotic use."

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- **Antibiotic Resistance in Animal Agriculture**: Research includes how antibiotic resistance in animal agriculture impacts livestock, the environment and the spreading of infectious diseases (pp. 2-9).
- **Swine**: Research includes how producing swine impacts air, water and farm workers (pp. 10-13).
- **Poultry**: Research includes how producing poultry impacts farm workers, public health and the spreading of antibiotic-resistant bacteria (pp. 14-18).
- **Retail Products**: Research includes how the food production system impacts the food supply (pp. 19-21).
- **MRSA**: Research includes how MRSA impacts certain areas across the country, veterinarians, health care employees and farmers (pp. 22-24).
- **Antimicrobial-Resistant Infections:** Research includes how infections are arising with implications toward the use of antimicrobials in food animal production (pp. 25-27).

ANTIBIOTIC RESISTANCE IN ANIMAL AGRICULTURE

The impacts of antibiotic resistance in animal agriculture on livestock, the environment and the spreading of infectious diseases.

Joint Committee on the use of antibiotics in animal husbandry and veterinary medicine ("Swann Report"). M.M. Swann, et al. Cmnd. 4190. London: Her Majesty's Stationery Office, 1969.

Summary: Reports on the status of antibiotic use in man and animals. Outlines the uses and amounts consumed for both. Reviews the reasons for which antibiotics are administered to food animals, including disease prevention, use in growth promotion, stress reduction and therapy. States that there are possible dangers to the human population stemming from the administration of antibiotics to animals, such as the rise of antibiotic-resistant strains of bacteria in animals that could cause disease in humans. The resulting infection could then be difficult to treat due to the null effect of antibiotics. Other dangers include the transmission of resistance determinants from animal strains to human strains of bacteria. It is known that such transfers take place and the fear is that resistance may be transferred to normal bacteria that inhabit the human bowel and/or to pathogens that may then cause disease. Discusses the prevalence of multiple antibiotic-resistant strains of bacteria and how they may arise. States that even though there are multiple antibiotics available for treatment of certain diseases, those reserved as a drug of choice may have a number of advantages over alternative treatment. Strains with multidrug resistance pose a greater threat in that the only effective drugs left for treatment in humans may be unsuitable because of toxicity or allergy. These infections are likely to arise where humans and animals share a pathogen such as *Salmonella* and the administration of antimicrobials to animals no doubt encourages the prevalence of resistance in these strains. Concludes that the use of antimicrobials in food animal production, especially when used in growth promotion, is of great concern and that limiting factors should be put in place to secure the use of antibiotics of greatest importance in human administration for therapeutic uses only and in some cases excluded from animal use altogether.

Changes in intestinal flora of farm personnel after introduction of a tetracycline-supplemented feed on a farm. S.B. Levy, G.B. Fitzgerald and A.B. Macone. *New England Journal of Medicine,* 1976. 295(11): 583-588.

Summary: Reports a study to determine if giving animals antibiotics in feed caused changes in intestinal bacterial flora and if workers and neighbors of the farm were affected. Chickens were screened for bacteria before and after a diet that included tetracycline-supplemented feed. Resistance to tetracycline changed dramatically within 36 to 48 hours of changing the diet of the animals. Within two weeks, 90 percent of the chickens were found to excrete essentially all tetracycline-resistant organisms. Within five to six months, there was a large increase in tetracycline-resistant bacteria in farm dwellers while the neighbors showed no change in bacterial count.

An epidemic of resistant *Salmonella* in a nursery: Animal-to-human spread. R.W. Lyons, C.L Samples, H.N. DeSilva, K.A. Ross, E.M. Julian and P.J. Checko. *Journal of the American Medical Association*, 1980. 243(6): 546-547.

Summary: Studies the case of a pregnant woman, infected with *Salmonella heidelberg*, who worked on her father's farm until four days before delivery. Her baby subsequently developed mild diarrhea, as did two others sharing the hospital nursery. *Salmonella heidelberg* was isolated from each and in all cases was resistant to chloramphenicol, sulfamethoxazole and tetracycline.

The strain was presumed to originate from a herd of infected dairy cows at the woman's father's farm as those bacteria showed the same resistance pattern as did those collected from the father.

Emergence of multidrug-resistant *Salmonella enterica* serotype Typhimurium DT104 infections in the United States. M.K. Glynn, C. Bopp, W. Dewitt, P. Dabney, M. Mokhtar and F.J. Angulo. *New England Journal of Medicine,* 1998. 338(19): 1333-1338.

Summary: Reviews *Salmonella* data collected by local and state health departments and public health laboratories between 1979 and 1996. Finds that a rapid increase of multidrug-resistant *Salmonella enterica* serotype typhimurium (DT104), a strain widely distributed in food animals and known to cause disease in humans, occurred in this period. The percentage rose from 0.6 percent in 1979–1980 to 34 percent in 1996. Concludes that more prudent use of antibiotics on farms is necessary to reduce the dissemination of multidrug-resistant *Salmonella* and emergence of further resistant strains.

Epidemiologic aspects, control, and importance of multiple-drug resistant *Salmonella* typhimurium DT104 in the United States. J.E. Akkina, A.T. Hogue, F.J. Angulo, R. Johnson, K.E. Petersen, P.K. Saini, P.J. Fedorka-Cray and W.D. Schlosser. *Journal of the American Veterinary Medical Association,* 1999. 214(6): 790-798.

Summary: Studies an animal strain of *Salmonella* and its prevalence of infection in humans. States that multidrug-resistant *Salmonella* DT104 is the second-most-prevalent *Salmonella* organism isolated from humans in England and Wales in the time frame of this study. Gives numerous examples of outbreaks in the U.S., most of which are traced to milk. Cattle, along with pigs, sheep, chickens, turkeys and several other animals, are known carriers of this strain.

Transfer of antibiotic resistant bacteria from animals to man. H.C. Wegener, F.M. Aarestrup, P. Gerner-Smidt and F. Bager. *Acta Veterinaria Scandinavica Supplementum*, 1999. 92: 51-57.

Summary: Describes zoonotic bacterial infections and their treatment. States that most *Salmonella, campylobacter, yersinia* and entero-haemorrhagic *E. coli* (EHEC) infections do not require antibiotic therapy, but in some cases these tools provide life-saving cures. Increasing levels of resistance in these bacteria, especially fluoroquinolone resistance, give rise for concern when it comes to human infections. Calls for infection control at the herd level and the need for prudent use of antibiotics in food animals.

Ceftriaxone-resistant *Salmonella* infection acquired by a child from cattle. P. Fey, T.J. Safranek, M.E. Rupp, E.F. Dunne, E. Ribot, P.C. Iwen, P.A. Bradford, F.J. Angulo and S.H. Hinrichs. *New England Journal of Medicine,* 2000. 342: 1242-1249.

Summary: Reports the case of a 12-year-old boy who lived on a farm in Nebraska and was infected with a ceftriaxone-resistant strain of *Salmonella enterica* serotype typhimurium that was traced to his father's herd of cattle using molecular techniques. States that this finding adds to the growing body of evidence suggesting that the use of antibiotics in livestock is the prominent source of resistance to these agents in *Salmonella* infection.

Appropriate regulation of antibiotics in livestock feed. R.L. Goforth and C.R. Goforth. *Boston College Environmental Affairs Law Review*, 2000. 28(1): 39-77.

Summary: Reviews nontherapeutic uses of antimicrobials in food animals and their impact on human health. States that this practice is creating possibly irreversible effects on the viability of

antibiotics used to treat human disease. Concludes that despite short-term economic benefits associated with the widespread use of antibiotics in agriculture, the risk to human health justifies a change in policy.

Antibiotic resistance in *Campylobacter* strains isolated from animals, foods and humans in Spain in 1997–1998. Y. Saenz, M. Zarazaga, M. Lantero, M.J. Gastaneres, F. Baquero and C. Torres. *Antimicrobial Agents and Chemotherapy,* 2000. 44(2): 267-271.

Summary: Studies *Campylobacter* isolated from foods, animals and humans. Finds that a high percentage of *Campylobacter jejuni* contaminates food (54.4 percent), broilers (81 percent) and pigs (88.9 percent). Isolates collected from broilers and pigs showed a 99 percent resistance rate to ciprofloxacin, with only a slightly lower number of human isolates (72 percent) also resistant. High resistance percentages to ampicillin, erythromycin, gentamicin and amikacin also were detected for *C. coli* isolated from these sources. Concludes that "more restrictive policies on the use of antibiotics in animals may result in an improvement of the current situation in the medium term."

The effect of banning avoparcin on VRE carriage in The Netherlands. A.E. van den Bogaard, N. Bruinsma and E.E. Stobberingh. *Journal of Antimicrobial Chemotherapy,* 2000. 46: 146-148.

Summary: Discusses the removal of avoparcin, an antimicrobial similar to vancomycin, from commercial food animal production in several settings. Sweden, which banned the use of antibiotics as growth promoters in 1986, has not reported any vancomycin-resistant *Enterococci* (VRE). This example strongly suggests that the removal of selective pressure will remove VRE from the human population over time. Denmark also banned the use of avoparcin in 1995 and saw the prevalence of poultry-isolated cases of VRE drop from greater than 80 percent in 1995 to less than 5 percent in 1998.

Epidemiology of resistance to antibiotics: Links between animals and humans. A. Van der Bogaard and E.E. Stobberingh. *International Journal of Antimicrobial Agents*, 2000. 14: 327-335.

Summary: Discusses the ban on avoparcin in food animals in the European Union and resulting significant decreases in resistance to vancomycin (a related drug) in intestinal *Enterococci* bacteria in animals and humans. States that resistant bacteria from animals can infect or reach the human population by direct contact and via food products of animal origin. Shows evidence for transfer of resistant genes between bacteria in humans and animals and recommends reducing the amount of antibiotics used in food animals in order to protect public health and safeguard the efficacy of antibiotics in veterinary medicine.

Quinolone and macrolide resistance in *Campylobacter jejuni* and *C. coli*: Resistance mechanisms and trends in human isolates. J. Engberg, F.M. Aarestrup, D.E. Taylor, P.Gerner-Smidt and I. Nachamkin. *Emerging Infectious Diseases,* 2001. 7(1):24-34.

Summary: Reviews the increasing resistance of *Campylobacter* strains to macrolide and quinolone antibiotics in human clinical isolates with respect to the use of these agents in food animals. Data suggest that while erythromycin and other macrolides should continue to be the antibiotics of choice in most regions, fluoroquinolones may be of limited use in many areas as the overuse of enrofloxacin and other drugs in food animals has caused a sharp upswing in the resistance of *Campylobacter* to these antibiotics.

The need to improve antimicrobial use in agriculture: Ecological and human health consequences. Alliance for the Prudent Use of Antibiotics. *Clinical Infectious Diseases*, 2002 supplement. 34 (S3): S71-144.

Summary: Reviews more than 500 studies relating to agricultural uses of antibiotics and concludes that "elimination of nontherapeutic use of antimicrobials in food animals and agriculture will lower the burden of antimicrobial resistance."

Potential mechanisms of increased disease in humans from antimicrobial resistance in food animals. M. Barza. *Clinical Infectious Diseases*, 2002. 34 (Suppl 3): S123-125.

Summary: Summarizes five potential mechanisms by which antimicrobial resistance may adversely affect human health. Two of the five relate to antimicrobial use in animals: (1) that resistant pathogens acquired by animals as the result of treatment with antibiotics transmit these pathogens through the food chain; and (2) that commensal flora of animals may acquire resistance traits from the previous pool of resistant pathogens, which then may be passed to human commensals and/or pathogens through the food chain.

Antimicrobial residues in animal waste and water resources proximal to large-scale swine and poultry feeding operations. E.R. Campagnolo, K.R. Johnson, A. Karpati, C.S. Rubin, D.W. Kolpin, M.T. Meyer, J.E. Estaban, R.W. Currier, K. Smith, K.M. Thu and M. McGeehin. *The Science of the Total Environment,* 2002. 299: 89-95.

Summary: Reports on data from numerous antimicrobial residues collected from animal wastes, surface water and groundwater proximal to large-scale swine and poultry operations. Data indicate that animal waste applied as fertilizer to the land may serve as a contaminating source of antimicrobial residues for the environment as a detectable level of antimicrobial compounds was found in waste-storage lagoons and surface and groundwater proximal to these operations.

Antimicrobial use and resistance in animals. S.A. McEwen, P.J. Fedorka-Cray. *Clinical Infectious Diseases*, 2002. 34 (Suppl 3): S93-106.

Summary: Describes antibiotic use in each animal class. Discusses a 1999 report on the economic effects of banning subtherapeutic antibiotic use in the U.S. Concludes that meat producers following good management practices would not be adversely affected by such a ban. Reviews antimicrobial-resistance-monitoring programs in bacteria of animal origin and the techniques involved. States alternatives to using antibiotics in food animals, such as providing good sanitation, air temperature, and clean water, as well as vaccine use and development and use of probiotics that consist of live, beneficial bacteria.

Emergence, spread and environmental effect of antimicrobial resistance: How use of an antimicrobial anywhere can increase resistance to any antimicrobial anywhere else. T.F. O'Brien. *Clinical Infectious Diseases*, 2002. 34(Suppl 3): S78-84.

Summary: Discusses how a bacterial community responds to antimicrobial use by obtaining resistance genes as well as how these genes are spread around the globe and between different bacterial populations. States that in Europe a ban of avoparcin, an antibiotic similar to vancomycin, was implemented in 1997 because of rising concerns that strains of vancomycin-resistant *Enterococci* were being used for growth promotion.

Generally overlooked fundamentals of bacterial genetics and ecology. A.O. Summers. *Clinical Infectious Diseases*, 2002. 34 (Suppl 3): S85-92.

Summary: Reviews how treatment with any given antibiotic may result in resistance to several antibiotics because of the ability of bacteria to obtain genetic elements that code for multidrug resistance. States that the exchange of bacteria between a host and its environment is a continual processand that selective pressure applied to any part of the ecosystem will result in a highly resistant bacterial population. Also states that once resistance is acquired it will be hard to reverse because of molecular mechanisms inherent in bacteria that ensure future generations hold on to resistance characteristics.

Human diseases caused by foodborne pathogens of animal origin. M.N. Swartz. *Clinical Infectious Diseases*, 2002. 34 (Suppl 3): S111-122.

Summary: Evaluates the likelihood that emergence of several resistant strains of bacteria occurred first in animals rather than humans. Reviews studies that correlate antimicrobial use on farms to the occurrence of colonization and infection of farm workers and residents of the surrounding communities. Discusses the trend in antibiotic resistance in commensal microorganisms and their opportunistic infection of hospitalized patients.

Antimicrobial resistance in livestock. B. Catry, H. Laevens, L.A. Devriese, G. Opsomer and A. Kruif. *Journal of Veterinary Pharmacology and Therapeutics*, 2003. 26: 81-93.

Summary: Reviews resistance in animals from a veterinary perspective. Notes that resistance could result in economic losses and animal welfare problems for livestock producers and that "the resistance level in a population is directly related to amount of antimicrobial drugs used." States that commensal bacteria in healthy animals fed or administered antibiotics contain resistance genes that if ingested by humans could colonize the gut and transfer these genes to pathogenic bacteria. This transfer would result in treatment difficulty because of antibiotic resistance.

Emergence of multidrug-resistant *Salmonella enterica* Serotype Newport infections resistant to expanded-spectrum cephalosporins in the United States. A. Gupta, et al. *Journal of Infectious Diseases*, 2003. 188: 1707-1716.

Summary: Discusses the emergence of new strains of multidrug-resistant *Salmonella* in New England. Reports that isolates of Newport-MDRAmpC among *Salmonella* serotype Newport from humans rose from 0 percent in 1998 to 53 percent in 2001. This strain shows resistance to amoxicillin/clavulanic acid, cephalothin, cefoxitin and ceftiofur. Concludes that the use of antimicrobial agents in livestock is linked to the emergence of antimicrobial-resistant nontyphoidal *Salmonella* and that the emergence of Newport-MDRAmpC strains in humans has coincided with the same infections in cattle.

Evidence of an association between use of anti-microbial agents in food animals and antimicrobial resistance among bacteria isolated from humans and the human health consequences of such resistance. F.J. Angulo, V.N. Nargund and T.C. Chiller. *Journal of Veterinary Medicine*, 2004. 51: 374-379.

Summary: Reviews antimicrobial-resistant infections occurring in humans as a result of antibiotic use in food animal production. States that "a review of outbreaks of *Salmonella* infections indicated that outbreaks were more likely to have a food animal source than outbreaks caused by anti-microbial-susceptible *Salmonella*." Reports that the human health consequences

resulting from bacterial resistance include infections caused by resistant pathogens, an increase in treatment failures and increased severity of disease.

Nontherapeutic use of antimicrobial agents in animal agriculture: Implications for pediatrics. K.M. Shea. *Pediatrics,* 2004. 114(3): 862-868.

Summary: Examines how antimicrobials are used in food animal production and how this practice could contribute to resistance in humans. Notes that children are at greater risk from resistant infections than the general population.

Antibiotic use in agriculture and its impact on the terrestrial environment. K. Kumar, S.C. Gupta, Y. Chander and A.K. Singh. *Advances in Agronomy*, 2005. 87: 1-54.

Summary: Discusses the impact of antibiotic use on disease treatment and growth promotion in animals. States that overuse of antibiotics results in the excretion of drugs that are not absorbed in the animal and that the resulting manure stock may be spread on fields, altering the soil bacteria and contaminating water sources. Notes that the continued prevalent use of antibiotics in agriculture is increasing the emergence of antibiotic-resistant bacteria both in both clinically relevant strains of pathogens and in normal commensal microorganisms. Concludes that "prudent use of antibiotics to a bare minimum along with alternative methods that minimize development and proliferation of resistant bacteria need investigation."

Agricultural antibiotics and human health: Does antibiotic use in agriculture have a greater impact than hospital use? D.L. Smith, J. Dushoff and J.G. Morris, Jr. *PLoS Medicine,* 2005. 2(8): 731-735.

Summary: Reviews the emergence and spread of antibiotic-resistant bacteria and notes that mathematical models can help with understanding underlying mechanisms and guiding policy responses. Agricultural antibiotic use may generate novel types of antibiotic-resistant bacteria that spread to humans; models can help estimate how much additional disease has been caused by agricultural antibiotic use. Depending on the assumptions used, the model suggests that transmission from agriculture can have a greater impact than hospital transmission on human populations.

The potential role of concentrated animal feeding operations in infectious disease epidemics and antibiotic resistance. M.J. Gilchrist, C. Greko, D.B. Wallinga, G.W. Beran, D.R. Riley and P.S. Thorne. *Environmental Health Perspectives*, 2007. 115(2): 313-316.

Summary: Reports the recommendations of a working group that was part of the 2005 *"Conference on Environmental Health Impacts of Concentrated Animal Feeding Operations: Anticipating Hazards – Searching for Solutions."* Recommendations include the following: discontinue nontherapeutic use of antibiotics as growth promoters; establish nationwide surveillance programs to fully assess the contribution of antibiotic use in livestock production to the creation of ecological reservoirs of resistance or the transmission of that resistance to humans; identify resistant strains; and establish minimum separation distances for swine and poultry facilities to reduce the risk of influenza outbreaks and municipal-style waste treatment to limit microbial and nutrient contamination of surface and groundwater.

Fluoroquinolone-resistant *Campylobacter* species and the withdrawal of fluoroquinolones from use in poultry: A public health success story. J.M. Nelson, T.M. Chiller, J.H. Powers and F.J. Angulo. *Clinical Infectious Diseases,* 2007. 44: 977-980.

Summary: Reviews fluoroquinolone use and the resulting effect of resistance occurring in the *Campylobacter* that followed the withdrawal of enrofloxacin from use in treating poultry. States that 13 percent of all resistant infections occur from travel abroad, showing that resistance is a global threat and that U.S. regulatory actions are not effective internationally. Concludes that "judicious use of antimicrobial agents should be stressed to preserve the efficacy of these important chemotherapeutic agents."

Environmental health impacts of concentrated animal feeding operations: Anticipating hazards—searching for solutions. P.S. Thorne. *Environmental Health Perspective,* 2007. 115: 296-297.

Summary: Outlines potential risks to human health from concentrated animal feeding operations (CAFOs) and the research needed to better understand the impact of these operations on public health. Examples of policy change include establishment of a requirement for minimum separation distances, use of solid-waste storage tanks to eliminate the possibility of microbial contamination spreading to water sources and provision of clean water sources for drinking. Expresses concerns over air quality and the need for better surveillance in this area. Expresses a need to phase out the use of antimicrobial agents as growth promotants.

Associations between antimicrobial resistance genes in fecal generic *Escherichia coli* isolates from cow-calf herds in western Canada. S.P. Gow, C.L. Waldner, J. Harel and P. Boerlin. *Applied and Environmental Microbiology,* 2008. 74(12): 3658-3666.

Summary: Studies antimicrobial-resistance gene distribution among cow-calf herds in western Canada. Finds that 65 percent of the 207 examined isolates of *E. coli* were resistant to at least one antimicrobial. Several patterns emerged from this research, suggesting that when a bacterium acquires resistance to one antimicrobial it is likely to become resistant to others because of the transfer of mobile genetic elements that harbor regions of multiple drug resistance. This suggests that even with careful restriction of antimicrobial use on farms, bacteria may still pick up resistance unrelated to the antimicrobials being used.

Industrial food animal production, antimicrobial resistance, and human health. E.K. Silbergeld, J. Graham and L.B. Price. *Annual Review of Public Health,* 2008. 29: 151-169.

Summary: Reviews the use of antimicrobials in agriculture and presents evidence for resistance stemming from their use in food animals. States that agricultural use of antibiotics can significantly shorten the useful life of these drugs, which are also used to treat disease in humans and animals. Suggests that estimates of nontherapeutic antibiotic use in agriculture fall between 60 percent and 80 percent of total antimicrobial production in the U.S. Concludes that "the use of antimicrobials for nontherapeutic purposes in agriculture is a major factor driving the emergence of antimicrobial resistance globally," and that "prudent public health policy thus indicates that nontherapeutic uses of antimicrobials in food animal production should stop."

Effect of subtherapeutic administration of antibiotics on the prevalence of antibiotic-resistant *Escherichia coli* bacteria in feedlot cattle. T.W. Alexander, L.J. Yanke, E. Topp, M.E. Olson, R.R. Read, D.W. Morck, T.A. McAllister. *Applied and Environmental Microbiology,* 2008. 74(14): 4405-4416.

Summary: A study of *E. coli* resistance in feedlot cattle when they were administered a sub-therapeutic level of antibiotics. Cattle previously not treated with antibiotics were brought to a

research feedlot where they were divided into groups each receiving a different regimen of sub-therapeutic antibiotics along with one group as a control not being treated. Cattle were fed two different diets during their treatments, one silage based diet and another grain based. Cattle tested before entering the feedlot (before starting sub-therapeutic treatment) were colonized with *E. coli* resistant to tetracycline (TET) at a rate greater than 40 percent, suggesting a colonization of TET resistant *E. coli* from birth (i.e. there is a high population of *E. coli* in circulation with TET resistance). Additionally the group fed chlortetracycline plus sulfamethazine (TET-SUL) showed an increased rate of TET resistance. A grain-based diet also appeared to increase not only the finding of *E. coli* but also increased the rate of finding TET resistant *E. coli*. Noted is that when antibiotic treatment was stopped for a period of about one to two months during each diet there was not a significant decline in the shedding of resistant *E. coli* except in the TET-SUL group where a slight decline was observed. However, upon starting treatment again the decline was reversed and prevalence of resistance continued to climb. The authors do note that in previous studies a decline in resistance has been shown when antibiotics (selective pressures) were removed from diets of animals, but this may sometimes take years to see a marked decrease. In summary feeding of certain diets and addition of certain sub-therapeutic levels of antibiotics in feed will increase the rate of resistance in *E. coli*.

The effects of transport and lairage on counts of *Escherichia coli* O157 in the feces and on the hides of individual cattle. N. Fegan, G. Higgs, L. Duffy and R.S. Barlow. *Foodborne Pathogens and Disease,* 2009. 6(9):1113-1120.

Summary: Reports on a study in which *E. coli* O157 rates from feces and from hides of cattle were monitored to determine whether a change occurred during transport from the feedlot to slaughter. Concludes that "transport and lairage did not lead to an increase in the number or isolation rate of *E. coli* O157 from cattle."

Sublethal antibiotic treatment leads to multidrug resistance via radical-induced mutagenesis. M.A. Kohanski, M. A. DePristo and J.J. Collins. *Molecular Cell,* 2010. 37:311-320

Summary: Looks at mutation rates of *E. coli* exposed to sublethal doses of different antibiotics. Finds that when sublethal doses of antibiotics were given, cell production of radical oxygen species (ROS) occurred, leading to mutations. ROS can damage DNA, causing a mutation in such a way that the cells may acquire resistance to classes of antibiotics different from those with which they are being treated. Gives a clinical example of incomplete treatment with antibiotics (e.g., a missed pill), but one could postulate that in food animal production, where subtherapeutic levels of antibiotics are given for the purpose of growth promotion, this event may also occur.

SWINE

Ways in which swine production affects air, water and farm workers.

An outbreak of multidrug-resistant, quinolone-resistant *Salmonella enterica* serotype typhimurium DT104. K. Molbak, D.L. Baggesen, F.M. Aarestrup, J.M. Ebbesen, J. Engberg, K. Frydendahl, P. Gerner-Smidt, A.M. Petersen and H.C. Wegener. *New England Journal of Medicine,* 1999. 341: 1420-1425.

Summary: Reviews a 1998 *Salmonella enterica* serotype typhimurium DT104 outbreak in Denmark. The outbreak had 25 confirmed cases, with 11 patients hospitalized and two deaths. Previous cases were resistant to five antibiotics; however, cases in this outbreak also were resistant to nalidixic acid and had reduced susceptibility to fluoroquinolones. Analysis traced the infection to a swine herd delivered to a slaughterhouse and the resulting retail pork was found to be the common food source.

Concentrated swine-feeding operations and public health: A review of occupational and community health effects. D. Cole, L. Todd and S. Wing. *Environmental Health Perspectives,* 2000. 108: 685-699.

Summary: Reviews the effects of industrial farms on community health. States that there are many potential routes of community exposure to industrial farming hazards and that people residing near swine farms may be exposed to these agents through pathways such as airborne contaminants produced by building ventilation fans, soil transport of microbes from land-applied wastes and leaking lagoons that contaminate groundwater. States that more research is needed to determine the far-reaching effects of industrial farms on community health.

Occurrence and diversity of tetracycline-resistance genes in lagoons and groundwater underlying two swine production facilities. J.C. Chee-Sanford, R.I. Aminov, I.J. Krapac, N. Garrigues-Jeanjean and R.I. Mackie. *Applied and Environmental Microbiology*, 2001. 67(4): 1494-1502.

Summary: States that 25 percent to 75 percent of antimicrobials administered to food animals are poorly absorbed in the gut and are excreted in feces. These unaltered substances are then applied to land by spreading of manure. Finds that a broad range of tetracycline-resistance genes occurred in two swine-waste lagoons and that upon release into the environment these genes can potentially mobilize and persist. Data suggest that the presence of the resistance genes is due to seepage and movement of groundwater underlying the lagoons and that it may be substantial, as resistance genes were found in a well 250 meters downstream of the lagoon sampled.

Productivity and economic effects of antibiotics used for growth promotion in U.S. pork production. G. Y. Miller, K. A. Algozin, P. E. McNamara, E. J. Bush. *Journal of Agricultural and Applied Economics*, 2003. 35(3): 469-482.

Summary: Studies the use of growth promoting antibiotics (GPA) in pork production. Finds that when GPA are removed from production operations that use less than four different rations (feed) there is a net decrease in return at sale of nine percent. However, when farms use greater than four different rations there is an increase in feed conversion without the use of antibiotics. Furthermore, when farms used greater than four different rations and applied GPA, feed conversion decreased. The authors state "our results imply that antibiotics used for growth promotion are of value mainly when four or fewer different rations are used in finishing."

Antimicrobial resistance in commensal flora of pig farmers. H. Aubrey-Damon, K. Grenet, P. Sall-Ndiaye, D. Che, E. Cordeiro, M.E. Bougnoux, E. Rigaud, Y. Le Strat, V. Lemanissier, L. Armand-Lefèvre, D. Delzescaux, J.C. Desenclos, M. Liénard and A. Andremont. *Emerging Infectious Diseases,* 2004. 10(5): 873-879.

Summary: Compares the carriage rates of antibiotic-resistant bacteria isolated from pig farmers and non-farmers matched for sex, age and county of residence in France. Finds that farmers carry a higher percentage of resistant commensal bacteria than non-farmers. States that the rate of VRE colonization did not differ between farmers and non-farmers and that this finding suggests that the 1997 ban of avoparcin was effective.

Airborne multidrug-resistant bacteria isolated from a concentrated swine feeding operation. A. Chapin, A. Rule, K. Gibson, T. Buckley and K. Schwab. *Environmental Health Perspectives*, 2005. 113: 137–142.

Summary: Reports the results of studies air samples taken within confined hog operations for antibiotic-resistant bacteria. Ninety-eight percent of bacteria sampled had resistance to at least two antibiotics used in animal production and a greater potential for worker exposure to resistant bacteria, suggesting that exposure to air from swine operations may allow multidrug-resistant bacteria to be transferred from animals to humans. Notes that "these data are especially relevant to the health of swine CAFO [concentrated animal feeding operations] workers, their direct contacts in the community, and possibly nearby neighbors of swine CAFOs."

Detection and occurrence of antimicrobially resistant *E. coli* in groundwater on or near swine farms in eastern North Carolina. M.E. Anderson and M.D. Sobsey. *Water Science and Technology,* 2006. 54(3): 211-218.

Summary: Compares the extent of groundwater contamination from antibiotic-resistant *E. coli* from industrial swine farms and reference sites. Sixty-eight percent of the *E. coli* from the swine farm sites were resistant to at least one antibiotic, while only one isolate from each of the reference sites showed resistance. Concludes that groundwater on or near swine farms may pose as an environmental pool for antibiotic-resistant *E. coli* and resistance genes.

The effect of subtherapeutic chlortetracycline on antimicrobial resistance in the fecal flora of swine. J.A. Funk, J.T. Lejeune, T.E. Wittum and P.J. Rajala-Schultz. *Microbial Drug Resistance*, 2006. 12(3): 210-218.

Summary: Studies the occurrence of antimicrobial-resistant *Salmonella* due to the subtherapeutic use of chlortetracycline in the diets of swine. Concludes that "there was a positive association between inclusion of subtherapeutic chlortetracycline in the diet and resistance to multiple antimicrobials."

Isolation of antibiotic-resistant bacteria from the air plume downwind of a swine confined or concentrated animal feeding operation. S.G. Gibbs, C.F. Green, P.M. Tarwater, L.C. Mota, K.D. Mena and P.V. Scarpino. *Environmental Health Perspectives*, 2006. 114: 1032–1037.

Summary: Studies air samples from upwind, downwind and inside of a confined hog operation. Bacterial samples were tested for antibiotic resistanceand *Staphylococcus aureus was* the dominant species recovered. Samples taken within the barn displayed the highest rate of resistance; samples taken up to 150 meters downwind of the barn showed a higher level of resistance than samples taken upwind. Multiple antibiotic-resistant organisms were also found

within and around the barn. Concludes that this increase in antimicrobial resistance could have a negative on the health of people who live around these facilities.

Community-acquired MRSA and pig-farming. X.W. Huijsdens, B.J. van Dijke, E. Spalburg, M.G. van Santen-Verheuvel, M.E. Heck, G.N. Pluister, A. Voss, W.J.B. Wannet and A.J. de Neeling. *Annals of Clinical Microbiology and Antimicrobials*, 2006. 5(26).

Summary: Reports a mother and baby who were found to be carriers of MRSA. A case study followed, finding that the father was a pig farmer, a screening was done to test coworkers, pigs and family members. Three coworkers, eight of 10 pigs and the father were found to be carriers of MRSA. Molecular characterization of the samples clearly revealed transmission of MRSA from pigs to humans. These findings show clonal spread and transmission of MRSA between humans and pigs in the Netherlands.

Are swine workers in the United States at increased risk of infection with zoonotic influenza virus? K.P. Myers, C.W. Olsen, S.F. Setterquist, A.W. Capuano, K.J. Donham, E.L. Thacker, J.A. Merchant and G.C. Gray. *Clinical Infectious Diseases,* 2006. 42: 14-20.

Summary: Studies farmers, meat-processing workers, veterinarians and a control group to determine the extent of exposure to pandemic influenza strains originating from pigs. Finds that farmers are at greatest risk and tend to demonstrate a higher titer to both H1N1 and H1N2 swine influenza virus isolates than control subjects do.

Risk factors for antimicrobial resistance among fecal *Escherichia coli* from residents on forty-three swine farms. T.H. Akwar, C. Poppe, J. Wilson, R.J. Reid-Smith, M. Dyck, J. Waddington, D. Shang, N. Dassie, and S.A. McEwen. *Microbial Drug Resistance*, 2007. 13(1): 69-76.

Summary: Focuses on residents and workers of hog operations that fed antibiotics and those that did not. *E. coli* was obtained from 115 residents and tested for resistance; 25.8 percent of *E. coli* sampled was resistant to at least one antibiotic. Prevalence of resistant bacteria was higher among workers or residents of the farms where antibiotics were fed to hogs. Results indicate that farmers have an increased occupational hazard of exposure to antibiotic-resistant bacteria when antibiotics are fed to animals.

Monitoring and source tracking of tetracycline resistance genes in lagoons and groundwater adjacent to swine-production facilities over a 3-year period. S. Koike, I.G. Krapac, H.D. Oliver, A.C. Yannarell, J.C. Chee-Sanford, R.I. Aminov and R.I. Mackie. *Applied and Environmental Microbiology,* 2007. 73(15): 4813-4823.

Summary: Studies the dissemination of tetracycline-resistance genes from lagoons into the surrounding environment. DNA was extracted and analyzed by real-time quantitative PCR showing a similarity of 99.8 percent for a selected resistance gene between collected groundwater sample DNA and that of the lagoons. States that this is clear evidence that animal waste seeping from lagoons can affect the environment by spreading resistance genes though groundwater contamination.

Antibiotic-resistant *Enterococci* and fecal indicators in surface water and groundwater impacted by a concentrated swine feeding operation. A.R. Sapkota, F.R. Curriero, K.E. Gibson and K.J. Schwab. *Environmental Health Perspectives*, 2007. 115(7): 104-1045.

Summary: Reviews the risks associated with exposure to manure-contaminated water sources by industrial farms. The authors could not obtain specific data on levels of antibiotics in swine feed because it was premixed and delivered by a contracted integrator, which had deemed antibiotic-usage data proprietary information. Reports that elevated levels of fecal indicators and antibiotic-resistant *Enterococci* were detected in water sources situated down-gradient from a swine facility compared with up-gradient surface water and groundwater. Concludes that "the presence of resistant bacteria in both drinking water and surface water sources contaminated by swine farms could contribute to the spread and persistence of both resistant bacteria and antibiotic resistance determinants in humans and the environment."

Antibiotic resistant bacterial profiles of anaerobic swine-lagoon effluent. J.P. Brooks and M.R. McLaughlin. *Journal of Environmental Quality,* 2009. 38: 2431-2437.

Summary: Focuses on three types of swine farms—farrowing, nursery and finisher. Antibiotic-resistant bacteria were screened for and isolated from all three types of farm lagoons. States that selective pressures appear to have an effect on the amount of resistant isolates recovered from swine-waste lagoons. Nursery lagoons appeared to be most contaminated, with antibiotic-resistant bacteria most likely due to the elevated use of antibiotics in these operations. Finisher farm lagoons contained the lowest concentration, signaling a lower use of antimicrobials in this environment.

Prevalence, numbers and characteristics of *Salmonella* spp. on Irish retail pork. D.M. Prendergast, S.J. Duggan, U. Gonzales-Barron, S. Fanning, F. Butler, M. Cormican and G. Duffy. *International Journal of Food Microbiology,* 2009. 131: 233-239.

Summary: Explores results of a survey of *Salmonella* in samples of pork from butcher shops and retail markets in Ireland and reports that it was found to contaminate 2.6 percent of samples assayed. *S. Typhimurium* was the dominant serotype found, at a rate of 85 percent; it is also one of the most frequently isolated serotypes from humans in the Irish population. Evidence of cross-contamination was found between samples, pointing to the need for good hygiene practices at the retail level.

Occurrence and persistence of erythromycin resistance genes (*erm*) and tetracycline resistance genes (*tet*) in waste treatment systems on swine farms. J. Chen, F. C. Michel Jr. S. Sreevatsan, M. Morrison, Z. Yu. *Microbial Ecology,* 2010.

Summary: This study focuses on how to control antibiotic resistance (AR) that is generated by use of antibiotics in confined animal feeding operations (CAFOs). The authors suggest there are two ways to control AR: reduce the use of antimicrobials on farms or find an effective way to minimize AR dissemination off farms by destroying or containing AR on farms. This study focuses on the latter of those two ways and looks to gain perspective on how well swine farms are containing antibiotic resistance by treating animal manure that is produced in CAFOs before it is being disseminated into the environment. Three swine farms were sampled with different types of waste treatment systems. Upon testing in various stages of waste clean up the authors find that "AR arising from swine-feeding operations can survive typical swine waste treatment processes" and call for treatments that are more functional in destroying AR on farms.

POULTRY

The effects of poultry production on farm workers, public health and the spread of antibiotic-resistant bacteria.

Direct transmission of *Escherichia coli* from poultry to humans. A.A. Ojenyiyi. *Epidemiology and Infection*, 1989. 103(3): 513-522.

Summary: Compares the resistance traits of *E.coli* collected from free-range poultry with those from poultry in a large-scale commercial facility. Reports that resistance to the antibiotics tested occurred only in those samples collected from birds in a commercial setting. Attendants from the commercial facilities also were found to contain resistant bacteria while samples from villagers in the community were negative. The authors also demonstrated that attendants contract bacteria from birds in their care by conducting a study where they infected birds with a known type of resistant *E. coli* and screened the attendants for the same bacteria.

Quinolone resistance in *Campylobacter* isolated from man and poultry following the introduction of fluoroquinolones in veterinary medicine. H.P. Endtz, G.J. Ruijs, B. van Klingeren, W.H. Jansen, T. van der Reyden and R.P. Mouton. *The Journal of Antimicrobial Chemotherapy*, 1991. 27(2): 199-208.

Summary: Reports the results of tests for quinolone resistance in 883 strains of *Campylobacter* bacteria isolated between 1982 and 1989 from human stool and poultry products. *Campylobacter* isolated from poultry increased in resistance from 0 percent to 14 percent in that time, while resistance in human isolates rose from 0 percent to 11 percent. Results suggest that the increase is mainly due to use of enrofloxacin, a fluoroquinolone, in poultry.

High-frequency recovery of quinupristin-dalfopristin-resistant *Enterococcus faecium* isolates from the poultry-production environment. J.R. Hayes, A.C. McIntosh, S. Qaiumi, J.A. Johnson, L.L. English, L.E. Carr, D.D. Wagner and S.W. Joseph. *Journal of Clinical Microbiology*, 2001. 39(6): 2298-2299.

Summary: Studies the extent of resistance to quinupristin-dalfopristin, a drug reserved for human use to treat vancomycin-resistant enterococci, in *Enterococcus faecium*. Finds that resistance to this antimicrobial ranged between 51 percent and 78 percent in isolates screened from the food-production environment.

Antibiotic resistance of faecal *Escherichia coli* in poultry, poultry farmers and poultry slaughterers. A.E. van den Bogaard, N. London, C. Driessen and E.E. Stobberingh. *Journal of Antimicrobial Chemotherapy*, 2001. 47:763-771.

Summary: Reports a survey of *E. coli* in poultry and workers who were in close contact with animals. Finds that the highest resistance rates were in turkeys, closely followed by broilers. Isolates collected from the laying-hen population were much lower, possibly because of the infrequent use of antibiotics in these animals. In the human population the same results followed, with turkey workers' isolates showing greater resistance than those from broilers or laying-hens. Results also strongly suggest the transmission of resistant clones and resistance plasmids of *E. coli* from broilers and turkeys to humans.

The dioxin crisis as experiment to determine poultry-related *Campylobacter enteritis*. A. Vellinga and F. Van Loock. *Emerging Infectious Diseases,* 2002. 8(1): 19-22.

Summary: Poultry was withdrawn in Belgium in June 1999 after a contaminant was found in feed. According to a model designed from the sentinel surveillance system, *Campylobacter* infections decreased by 40 percent during that month—from 153 cases per week to 94 cases. States that by using the ban as an epidemiologic tool, the rate of *Campylobacter* infections attributable to poultry was determined to be greater than 40 percent.

The effect of withdrawing growth promoting antibiotics from broiler chickens: A long-term commercial industry study. H.M. Engster, D. Marvil, B. Stewart-Brown. *The Journal of Applied Poultry Research,* 2002. 431-436.

Summary: A comprehensive study where removal of growth promoting antibiotics (GPA) from broiler chickens was compared with those still receiving GPA. Average reduction of livability was only 0.2 percent on the Delmarva Peninsula (DMV) and 0.14 percent in North Carolina (NC). However, fluctuations were noted in livability from a reduction of 0.5 percent to a positive impact on livability of 0.3 percent. The average reduction in body weight was 0.03 lb on DMV and 0.04 lb in NC but this decline did not start until after the first year of the trial. Feed conversion (weight of food/body weight gain) was not adversely affected in the study for either location. Removal of GPA also resulted in no reports of field outbreaks of disease and total farm condemnations were not affected.

Fluoroquinolone-resistant *Campylobacter* isolates from conventional and antibiotic-free chicken products. L.B. Price, E. Johnson, R. Vailes and E. Silbergeld. *Environmental Health Perspectives,* 2005. 113: 557-560.

Summary: Concludes that there is no difference in *Campylobacter* contamination between conventionally raised chickens and poultry raised antibiotic-free; however, conventionally raised poultry is more likely to be resistant to antibiotics than chickens raised antibiotic-free. The findings also suggest that fluoroquinolone-resistant isolates of *Campylobacter* may persist after the usage of fluoroquinolones in poultry production has ceased.

Similarity between human and chicken *Escherichia coli* isolates in relation to ciprofloxacin resistance status. J.R. Johnson, M.A. Kuskowski, M. Menard, A. Gajewski, M. Xercavins and J. Garau. *The Journal of Infectious Diseases,* 2006. 194(1): 71-78.

Summary: Studies the similarities of *E. coli* isolates collected from humans and chickens that were resistant to ciprofloxacin. Finds that resistant *E. coli* in humans appears to have a profile similar to that of resistant *E. coli* collected from chickens, suggesting that the use of antimicrobials in poultry production is leading to resistant *E. coli* that are being transferred to humans, possibly though contaminated meats.

Use of streptogramin growth promoters in poultry and isolation of streptogramin-resistant *Enterococcus faecium* from humans. A.L. Kieke, M.A. Borchardt, B.A. Kieke, S.K. Spencer, M.F. Vandermause, K.E. Smith, S.L. Jawahir and E.A. Belongia. *The Journal of Infectious Diseases,* 2006. 194(9): 1200-1208.

Summary: Examines virginiamycin use in poultry and its effect on cross-resistance to quinupristin-dalfopristin, a drug also in the streptogramin category that is intended for treating vancomycin-resistant *Enterococcus faecium* infections in humans. The study enrolled patients

from hospitals and vegetarians and compared the samples from humans with samples collected from retail poultry meats. Reports that "poultry exposure is associated with a quinupristin-dalfopristin resistance gene and inducible quinupristin-dalfopristin resistance in human fecal *E. faecium*. The continued use of virginiamycin may increase the potential for streptogramin-resistant *E. faecium* infection in humans."

Subtherapeutic tylosin phosphate in broiler feed affects *Campylobacter* on carcasses during processing. M.E. Berrang, S.R. Ladely, R.J. Meinersmann and P.J. Fedorka-Cray. *Poultry Science*, 2007. 86:1229-1233.

Summary: Studies cross-resistance of tylosin and erythromycin (both macrolide drugs). Erythromycin is often the drug of choice for treating campylobacteriosis, and tylosin is approved at subtherapeutic levels for use in broiler feed for growth promotion. Seventy chicks were divided into two groups, half raised on tylosin, half without. Carcasses of broilers fed tylosin had lower numbers of *Campylobacter*, but all the *Campylobacter* found were resistant to erythromycin. No *Campylobacter* isolated from the control carcasses were resistant. Concludes that application of tylosin phosphate in feed results in lower numbers of *Campylobacter*, but those that remain are resistant to erythromycin.

Growth promoting antibiotics in food animal production: An economic analysis. J.P. Graham, J.J. Boland and E. Silbergeld. *Public Health Reports*, 2007. 122:79-87.

Summary: Examines the economic effect of removing antibiotics used for growth promotion in broiler chickens using data published by Perdue. Positive production changes were associated with use, but were insufficient to offset the cost of the antibiotics. The net effect of using growth-promoting antibiotics was a lost value of $.0093 per chicken (about 0.45 percent of total cost).

Development of macrolide-resistant *Campylobacter* in broilers administered subtherapeutic or therapeutic concentrations of tylosin. S.R. Ladely, M.A. Harrison, P.J. Fedorka-Cray, M.E. Berrang, M.D. Englen and R.J. Meinersmann. *Journal of Food Protection*, 2007. 70(8):1915-1951.

Summary: Looks at the impact of antibiotic use on increasing the amount of resistant bacteria in an environment. Poultry were divided into groups of 25 birds: the treatment group was given either therapeutic or subtherapeutic doses of tylosin beginning at two weeks of age while the control group was isolated and not given any antimicrobials. The animals fed subtherapeutic and therapeutic doses of tylosin tested positive for resistant bacteria; no resistant strains were found among the birds that did not get treated with tylosin. The birds treated with subtherapeutic doses of tylosin also showed increased resistance compared with the birds treated with therapeutic doses.

Elevated risk of carrying gentamicin-resistant *Escherichia coli* among U.S. poultry workers. L.B. Price, J.P. Graham, L.G. Lackey, A. Roess, R. Vailes and E. Silbergeld. *Environmental Health Perspectives*, 2007. 15(12):1738-1742.

Summary: Examines poultry workers and residents on the eastern shore of Maryland and Virginia. Poultry workers had 32 times the odds of being colonized with gentamicin-resistant *E. coli* as community residents; the poultry workers also had an elevated risk of carrying multidrug-resistant *E. coli*. Concludes that "occupational exposure to live animals in the broiler chicken industry may be an important route of entry for antimicrobial-resistant bacteria in to the community."

Antimicrobial resistance of old and recent *Staphylococcus aureus* isolates from poultry: First detection of livestock-associated methicillin-resistant strain ST398. M. Nemati, K. Hermans, U. Lipinska, O. Denis, A. Deplano, M. Struelens, L.A. Devriese, F. Pasmans and F. Haesebrouck. *Antimicrobial Agents and Chemotherapy*, 2008. Oct: 3817-3819.

Summary: Compares the resistance profiles of *Staphylococcus aureus* isolates collected from chickens in the 1970s with profiles from healthy chickens in 2006. Finds that resistant levels to eight of the drugs tested were significantly greater in the 2006 samples.

Food animal transport: A potential source of community exposures to health hazards from industrial farming (CAFOs). A.M. Rule, S.L. Evans and E.K. Silbergeld. *Journal of Infection and Public Health*, 2008. 1(1): 33-39.

Summary: Compares air samples collected while cars with bacterial-collection equipment were driven behind poultry transport vehicles with background samples taken during normal driving conditions. Twenty-five percent of samples collected while following poultry transport vehicles were resistant at least one antimicrobial, while all background samples were susceptible. Suggests that open-air poultry transport vehicles may play a role in spreading resistant bacteria that originated from the administration of antimicrobials to food animals.

Relationships between multidrug-resistant *Salmonella enterica* Serovar Schwarzengrund and both broiler chickens and retail chicken meats in Japan. T. Asai, K. Murakami, M. Ozawa, R. Koike and H. Ishikawa. *Japanese Journal of Infectious Diseases*, 2009. 62: 198-200.

Summary: A *Salmonella* strain that causes invasive salmonellosis in humans was isolated from broiler chickens and retail chicken meats in Japan. Numerous isolates showed multidrug resistance.

Fate of antimicrobial-resistant *Enterococci* and *Staphylococci* and resistance determinants in stored poultry litter. J.P. Graham, S.L. Evans, L.B. Price and E.K. Silbergeld. *Environmental Research*, 2009. 109: 682-689.

Summary: Studies the storage of poultry litter and the stability of bacteria and resistance genes during storage. Finds that over a 120-day period, typical storage practices of poultry litter are not sufficient for eliminating drug-resistant *Enterocci* and *Staphylococci*, which may then be delivered to the environment by land application, aerosolization or water contamination during runoff.

Antibiotic-resistant *Enterococci* and *Staphylococci* isolated from flies collected near confined poultry feeding operations. J.P. Graham, L.B. Price, S.L. Evans, T.K. Graczyk and E.K. Silbergeld. *Science of the Total Environment*, 2009. 407(8): 2701-2710.

Summary: Investigators collected poultry litter and trapped flies around poultry farms to determine the extent of bacteria present and their resistance-gene profile. Results suggest that flies around poultry operations harbor resistant bacteria in their digestive tracts and exterior surfaces. This could result in human exposure to resistant bacteria that arise from antimicrobial use on poultry farms. Highlights the persistence of resistant genes in the environment and the pool of resistance associated with the use of antibiotics in feed additives.

***Salmonella Heidelberg* Ceftiofur-related resistance in human and retail chicken isolates.** Public Health Agency of Canada. 2009.

Summary: In response to public health concerns about the rise of resistance in isolates of *Salmonella* and *E. coli* to ceftiofur, all broiler chicken hatcheries in Québec voluntarily stopped using ceftiofur in February 2005. This publication reports a decrease in the number of ceftiofur-resistant isolates in both chicken and human *S. heidelberg* isolates and in chicken *Escherichia coli* following the voluntary withdrawal of ceftiofur in hatching and day-old chicks in Québec.

Ceftiofur resistance in *Salmonella enterica* Serovar Heidelberg from chicken meat and humans, Canada. L. Dutil, R. Irwin, R. Finley, L. King Ng, B. Avery, P. Boerlin, A. Bourgault, L. Cole, D. Daignault, A. Desruisseau, W. Demczuk, L. Hoang, G.B. Horsman, J. Ismail, F. Jamieson, A. Maki, A. Pacagnella and D.R. Pillai. *Emerging Infectious Diseases*, 2010. 16(1): 48-54.

Summary: Studies *Salmonella* Heidelberg, a frequently reported cause of infections in North America with sources linked to consumption of poultry, eggs or egg-containing products. Compares resistance rates of *Salmonella* Heidelberg isolates collected from retail chicken to ceftiofur, a third-generation cephalosporin, with rates of human infections that also were resistant to ceftiofur during a period from 2003 to 2008. During this time frame ceftiofur was removed from extralabel use in chicken hatcheries in Québec, resulting in a dramatic decrease in ceftiofur resistance in *Salmonella* Heidelberg and *E. coli* in retail chicken. A similar decrease is shown in resistant human infections of *Salmonella* Heidelberg. Suggests that managing ceftiofur use at the hatchery level may control resistance rates to extended-spectrum cephalosporins. A partial reintroduction of ceftiofur use in hatcheries in 2007 caused a rise in ceftiofur resistance in *E. coli*, but at lower levels than those seen in 2003 to 2004.

Veterinary pharmaceuticals and antibiotic resistance of Escherichia coli isolates in poultry litter from commercial farms and controlled feeding trials. V. Furtula, E.G. Farrell, F. Diarrassouba, H. Rempel, J. Pritchard, M.S. Diarra. *Poultry Science*, 2010. 89:180-188.

Summary: This study found that there were antimicrobial residues in broiler litter from both a controlled environment, where chickens were fed a diet of feed with additives of bacitracin, chlortetracycline, monensin, narasin, nicarbazin, penicillin, salinomycin and virginiamycin and from commercial farms where the same feed additives were also used. Antimicrobials are not fully absorbed by animals in some cases and will be excreted into the litter leaving a residue of antibiotics that may then be applied to soil for crop fertilization. If application occurs, soil microbes will be subjected to these antibiotic pressures and may develop resistance themselves. There is also evidence for plants to uptake antimicrobial agents and can become a source of exposure to such compounds. *E. coli* isolates were collected from poultry litter from commercial farms and were found to be resistant to at least seven different antibiotics. Isolates from commercial farms showed a higher rate of resistance possibly due to the frequent use of feeds that are available with multiple antibiotics incorporated causing increased resistance. Resistance to such antibiotics as trimethoprim-sulfamethoxazole from isolates collected on commercial farms is of concern as this is a leading treatment of urinary tract infections.

RETAIL PRODUCTS

How industrial food animal production affects the food supply.

An evaluation of methods to assess the effect of antimicrobial residues on the human gut flora. D. Corpet. *Veterinary Microbiology,* 1993. 35(3-4):199-212.

Summary: Reviews the effects of antimicrobial residues on the human gut flora and concludes that "most resistant enterobacteria in the human gut of untreated people come from bacterial contamination of raw foods." This assumption stems from a study previously completed by the author in which a sterile diet was given to seven healthy volunteers with an outcome of reduced antibiotic-resistant bacteria in stools.

Quinoline-resistant *Campylobacter jejuni* infections in Minnesota, 1992–1998. K.E. Smith, J.M. Besser, C.W. Hedberg, F.T. Leano, J.B. Bender, J.H. Wickland, B.P. Johnson, K.A. Moore and M.T. Osterholm. *New England Journal of Medicine*, 1999. 340(20):1525-1532.

Summary: Reports that ciprofloxacin-resistant *C. jejuni* was isolated from 14 percent of 91 domestic chicken products obtained from retail markets in 1997. The number of quinolone-resistant infections acquired domestically has increased, largely because of the acquisition of resistant strains from poultry. Resulting infections may require additional antimicrobial therapy, as fluoroquinolones such as ciprofloxacin are commonly prescribed for diarrheal illnesses caused by *Campylobacter jejuni.*

Isolation of antimicrobial-resistant *Escherichia coli* from retail meats purchased in Greater Washington, DC, USA. C.M. Schroeder, D.G. White, B. Ge, Y. Zhang, P.F. McDermott, S. Ayers, S. Zhao, J. Meng. International Journal of Food Microbiology, 2003. 85: 197-202.

Summary: Retail meat samples were collected and analyzed from the DC area for presence of *E. coli.* Data on resistance to 11 antimicrobials are given with a large portion showing resistance to such antibiotics as tetracycline (59 percent), sulfamethoxazole (45 percent), streptomycin (44 percent), ampicillin (35 percent) and gentamicin (12 percent). The authors conclude that their findings suggest retail meats may often be contaminated with resistant *E. coli.*

Concurrent quantitation of total *Campylobacter* and total ciprofloxacin-resistant *Campylobacter* loads in rinses from retail raw chicken carcasses from 2001 to 2003 by direct plating at 42 degrees Celsius. R. Nannapaneni, R. Story, K.C. Wiggins and M.G. Johnson. *Applied and Environmental Microbiology*, 2005. 71(8): 4510-4515.

Summary: Analyzes the total amount of *Campylobacter* present in retail chicken as well as in ciprofloxacin-resistant isolates. Finds that ciprofloxacin-resistant *Campylobacter* persisted throughout the two-and-a-half-year study, showing a reservoir of resistance in the U.S. food market.

Sulfamethazine uptake by plants from a manure-amended soil. H. Dolliver, K. Kumar and S. Gupta. *Journal of Environmental Quality,* 2007. 36:1224-1230.

Summary: Studies the uptake of sulfamethazine, an antibiotic extensively used in animal agriculture for therapeutic and subtherapeutic purposes, in corn, lettuce and potatoes when manure-amended soil is used as the growing medium. Following 45 days of growth, all plants tested were contaminated with the antibiotic in varying concentrations.

Antimicrobial drug-resistant *Escherichia coli* from humans and poultry products, Minnesota and Wisconsin, 2002–2004. J.R. Johnson, M.R. Sannes, C. Croy, B. Johnston, C. Clabots, M.A. Kuskowski, J. Bender, K.E. Smith, P.L. Winokur and E.A. Belongia. *Emerging Infectious Diseases,* 2007, 13(6): 838-846.

Summary: Studies susceptible and resistant *E. coli* collected from hospital patients, healthy vegetarians and poultry that were raised conventionally and without antibiotics. Suggests that many resistant human isolates may originate from poultry. Isolates from healthy vegetarians also follow this pattern, suggesting that avoidance of poultry consumption does not decrease the possibility of carrying drug-resistant *E. coli* from poultry.

The isolation of antibiotic-resistant *Salmonella* from retail ground meats. D.G. White, S. Zhao, R. Sudler, S. Ayers, S, Friedman, S. Chen, P.F. McDermott, S. McDermott, D.D. Wagner and J. Meng. *New England Journal of Medicine*, 2007. 345(16):1147-1154.

Summary: Researchers tested *Salmonella* from samples of ground chicken, pork, beef and turkey purchased at three supermarkets in the Washington, DC, area. Of 200 samples, 41 (20 percent) contained *Salmonella*. Eighty-four percent of those were resistant to at least one antibiotic and 53 percent were resistant to at least three antibiotics. Sixteen percent were resistant to ceftriaxone, the drug of choice for treating salmonellosis in children.

Resistance in bacteria of the food chain: Epidemiology and control strategies. F.M. Aarestrup, H.C. Wegener and P. Collignon. *Expert Reviews,* 2008. 6(5): 733-750.

Summary: Reviews bacterial resistance due to the use of antimicrobials in food animals and their transferability to humans in the form of pathogens. States that limiting the selective pressure in food animal production, especially those antibiotics that are critically important to human health, will help control the emergence of resistant bacteria most efficiently.

Molecular analysis of *Escherichia coli* from retail meats (2002–2004) from the United States National Antimicrobial Resistance Monitoring System. J.R. Johnson, J.S. McCabe, D.G. White, B. Johnston, M.A. Kuskowski and P. McDermott. *Clinical Infectious Diseases,* 2009. 49: 195-201.

Summary: Researchers screened 287 *E. coli* isolates collected by the National Antimicrobial Resistance Monitoring System (NARMS) for virulence-associated genes. Resistant and susceptible strains differed minimally based on the assessed virulence factors; however, the four meat types screened showed a great variance as chicken and turkey isolates had consistently higher virulence scores than beef and pork samples. These results support the hypothesis that antimicrobial-resistant *E. coli* in retail meats emerge from a host species-specific lineage due to the direct effect of selection pressure from use of antimicrobials or as part of the organisms' adaptations to their respective hosts.

Transient intestinal carriage after ingestion of antibiotic-resistant *Enterococcus faecium* from chicken and pork. T.L. Sorensen, M. Blom, D.L. Monnet, N. Frimodt-Moller, R.L. Poulsen and F. Espersen. *New England Journal of Medicine,* 2009. 345(16): 1161-1166.

Summary: Reports on a study designed to test the ability of *Enterococci* from various meat sources to have sustained viability in the human intestine. Twelve volunteers ingested a suspension of *Enterococci* that originated from either a pig or chicken source that was resistant to at least one antibiotic. None of the 12 volunteers was colonized with resistant *Enterococci* at the onset of the experiment; however, eight of the 12 had antibiotic-resistant *Enterococci* isolated at

six days following ingestion, and one had resistant *Enterococci* at 14 days' post ingestion. Concludes that ingestion of resistant *Enterococci* of animal origin leads to detectable concentrations of the same resistant strain in stools for up to 14 days.

Methicillin-resistant *Staphylococcus aureus* in food products: Cause for concern or complacency? J. A. J. W. Kluytmans. Clinical Microbiology and Infection, 2010. 16(1): 11-15.

Summary: A review on an emerging sequence type of MRSA ST398, which has been isolated from various food animals. A recent study in the U.S. observed a contamination rate of 39.2 percent for *S. aureus* on retail meats and in that group 5 percent was MRSA. Studies abroad have shown rates of MRSA contaminating retail meats as high as 11.9 percent. The author suggests that even though ST398 does not appear to spread easily among humans this assumption needs to be confirmed in well-designed studies. The spread of ST398 from animals to humans needs to be monitored as the potential threat from the retail food reservoir has widespread potential implications on human health.

MRSA

The impacts of methicillin-resistant Staphylococcus aureus *(MRSA) on certain areas across the country, veterinarians, health care employees and farmers.*

Methicillin-resistant *Staphylococcus aureus* in pig farming. A. Voss, F. Loeffen, J. Bakker, C. Klaassen and M. Wulf. *Emerging Infectious Diseases*, 2005. 11(12): 1965-1966.

Summary: Examines cases of MRSA colonization resulting from farmers' contact with pigs, how it moved though their families and was transmitted between a hospital patient and nurse. Reports that the frequency of MRSA among the group of regional pig farmers is more than 760 times higher than that among the general Dutch population.

Methicillin-resistant *Staphylococcus aureus* colonization in veterinary personnel. B.A. Hanselman, S.A. Kruth, J. Rousseau, D.E. Low, B.A. Willey, A. McGeer and J.S. Weese. *Emerging Infectious Diseases*, 2006. 12(12): 1933-1938.

Summary: Reports a comprehensive evaluation of veterinary personnel for carriage of MRSA. Samples were taken from participants who resided in 19 different countries and rates of colonization were determined. Of the volunteers, 6.5 percent were positive for MRSA; those working with larger animals showed higher carriage rates (15.6 percent).

Hospitalizations and deaths caused by methicillin-resistant *Staphylococcus* aureus, United States, 1999–2005. E. Klein, D.L. Smith and R. Laxminarayan. *Emerging Infectious Diseases,* 2007. 13(12): 1840-1846.

Summary: Reports on trends in MRSA infections between 1999 and 2005. The estimated rise in hospitalizations due to *Staphylococcus aureus* infections during this time was 62 percent, while the rate of MRSA infections more than doubled.

Invasive methicillin-resistant *Staphylococcus aureus* infections in the United States. R.M. Klevens, M.A. Morrison, J. Nadle, S. Petit, K. Gershman, S. Ray, L.H. Harisson, R. Lynfield, G. Dumyati, J.M. Townes, A.S. Craig, E.R. Zell, G.E. Fosheim, L.K. McDougal, R.B. Carey and S.K. Fridkin. *Journal of the American Medical Association*, 2007. 285(15):1763-1771.

Summary: Finds that MRSA affects certain populations disproportionately, particularly African Americans. After researching invasive MRSA infections reported in hospitals in eight U.S. cities and the state of Connecticut, the authors estimate that in 2005 more than 94,000 cases of such infections occurred, 18,650 of which were fatal.

Emergence of methicillin-resistant *Staphylococcus aureus* of animal origin in humans. I. van Loo, X. Huijsdens, E. Tuemersma, A. de Neeling, N. van de Sande-Bruinsma, D. Beaujean, A. Voss and J. Kluytmans. *Emerging Infectious Diseases*, 2007. 13(12):1834-1839.

Summary: Reports that a new type of MRSA from an animal reservoir (pigs in the Netherlands) has recently entered the human population and is now responsible for greater than 20 percent of all MRSA in the Netherlands. As most nontypable MRSA isolates are resistant to doxycycline, the spread of MRSA may be facilitated by the abundant use of tetracyclines in pig and cattle farming.

Methicillin-resistant *Staphylococcus aureus* ST398 in humans and animals, Central Europe. W. Witte, B. Strommenger, C. Stanek and C. Cuny. *Emerging Infectious Diseases*, 2007. 13(2): 255-258.

Summary: Studies recent human colonization by MRSA ST398, which in previous years had not been seen in humans. Animal-to-human transmission may occur with this strain; for example, a dog being treated for a wound infection transmitted ST398 to the staff of the veterinary practice where the dog was treated. Concludes that "MRSA exhibiting ST398 may colonize and cause infections in humans and in certain animal species such as dogs, horses and pigs."

Methicillin-resistant *Staphylococcus aureus* colonization in pigs and pig farmers. T. Khanna, R. Friendship, D. Dewey and J.S. Weese. *Veterinary Microbiology,* 2008. 128:298-303.

Summary: This study, the first of MRSA and pig farms in Canada, found that the prevalence of MRSA colonization on pig farms was 45 percent; prevalence in pig farmers was 20 percent. Humans residing on farms where pigs were free of MRSA also tested negative for MRSA. The authors note another study in which MRSA was identified in food products intended for human consumption, but none originated in pigs. This study adds support to the hypothesis that MRSA can be transmitted between pigs and humans.

Pigs as source of methicillin-resistant *Staphylococcus aureus* CC398 infections in humans, Denmark. H.C. Lewis, K. Molbak, C. Reese, F.M. Aarestrup, M. Selchau, M. Sorum and R.L. Skov. *Emerging Infectious Diseases,* 2008. 14(9): 1383-1389.

Summary: Provides evidence that persons exposed to animals on farms in Denmark, particularly pig farms, have an increased chance of being colonized or infected with MRSA CC398.

Methicillin-resistant and -susceptible *Staphylococcus aureus* sequence type 398 in pigs and humans. A.van Belkum, D.C. Melles, J.K. Peeters, W.B. van Leeuwen, E. van Duijkeren, X.W. Huijsdens, E. Spalburg, A.J. de Neeling and H.A. Verbrugh. *Emerging Infectious Diseases*, 2008. 14(3):479-483.

Summary: Reports that MRSA ST398, primarily a pathogen of pigs, appears to be quite virulent and can cause bacteremia in humans. States that if MRSA ST398 obtains this pathogenicity, care should be taken not to introduce this strain into humans.

Transmission of methicillin-resistant *Staphylococcus aureus* strains between different kinds of pig farms. E. van Duijkeren, R. Ikawaty, M.J. Broekhuizen-Stins, M.D. Jansen, E.C. Spalburg, A.J. de Neeling, J.G. Allaart, A.van Nes, J.A.Wagenaar and A.C. Fluit. *Veterinary Microbiology,* 2008. 126: 383-389.

Summary: MRSA strains were found in 23 percent of the farms tested. States that the use of standard antimicrobials "seems to be a risk factor for finding MRSA-positive pigs on a farm. Pig farms on which the pigs were treated with antimicrobials as group medication had a higher risk of being MRSA positive, whereas farms on which antimicrobials were used restrictively had a much lower chance of being MRSA positive."

Increase in a Dutch hospital of methicillin-resistant *Staphylococcus aureus* related to animal farming. M.M.L. van Rijen, P.H. Van Keulen and J.A. Kluytmans. *Clinical Infectious Diseases*, 2008. 16:261-263.

Summary: Reports on a study 2002–2006 in the Netherlands involving hospital patients who had MRSA. Patients exposed to pigs or veal calves were shown to be at higher risk for MRSA as there was an emergence of nontypable MRSA during this time. Nontypable MRSA is assumed to stem from pigs and calves.

Methicillin-resistant *Staphylococcus aureus* (MRSA) strain ST398 is present in Midwestern U.S. swine and swine workers. T.C. Smith, M.J. Male, A.L. Harper, J.S. Kroeger, G.P. Tinkler, E.D. Moritz, A.W. Capuano, L.A. Herwaldt and D.J. Diekema. *PLoS ONE,* 2009. 4(1): e4258.

Summary: Investigates MRSA in the Midwestern U.S. Samples were taken from swine and production workers in two commercial operations. MRSA prevalence was 49 percent in swine and 45 percent in workers. Results show that MRSA is common in swine production in the U.S. and that these animals could be harboring the bacterium.

Methicillin-resistant *Staphylococcus aureus*: A new zoonotic agent? B. Springer, U. Orendi, P. Much, G. Hoger, W. Ruppitsch, K. Krziwanek, S. Metz-Gercek and H. Mittermayer. *The Middle European Journal of Medicine,* 2009. 121: 86-90.

Summary: Discusses changes in MRSA over the past decade. Once known almost completely as a hospital pathogen, MRSA is now emerging in the community in persons without hospital-related risk factors. Recent evidence also has shown a link between livestock colonization and MRSA infections in persons working with these animals. Identifies three potential transmission routes of MRSA: from animal origin into the population; human-to-human contact from farm workers to the community; via food or by environmental contamination.

Methicillin resistant Staphylococcus aurues ST398 in veal calf farming: Human MRSA carriage related with animal antimicrobial usage and farm hygiene. H. Graveland, J.A. Wagenaar, H. Heesterbeek, D. Mevius, E. van Duijkeren, D. Heederik. *PLoS One,* 2010. 5(6): 1-6.

Summary: Studies MRSA ST398 carriage in veal calves, farmers, their family members and employees. A large sampling size of veal calf farms in the Netherlands was selected at random to be screened for ST398. All participants were given a questionnaire to fill in describing their contact and role on the farm as well as how farm operations were conducted. Samples from both humans and veal calves were cultured and categorized using molecular techniques. The data presented show that direct associations between human and animal carriage of MRSA ST398 exist and that carriage was shown to increase in calves as antibiotic use on the farm increased. Duration of contact to veal calves showed a highly elevated risk of MRSA ST398 carriage in humans and a decrease in MRSA was seen in farms with better hygiene practices (ie cleaning of stables before new claves were brought on the farm). Disinfection was applied in less than 20 percent of the farms in the study and was not associated with prevalence of MRSA carriage in calves. Overall the prevalence of MRSA was 15.9 percent in participants who lived or worked on veal calf farms, which is far greater than the general population carriage rate in the Netherlands estimated to be below 1 percent.

ANTIMICROBIAL-RESISTANT INFECTIONS

Infections arising with implications toward the use of antimicrobials in food animal production.

Widespread distribution of urinary tract infections caused by a multidrug-resistant *Escherichia coli* clonal group. A.R. Manges, J.R. Johnson, B. Foxman, T.T. O'Bryan, K.E. Fullerton and L.W. Riley. *New England Journal of Medicine,* 2001. 345(14): 1007-1013.

Summary: Studies urinary tract infections (UTIs) in the U.S. caused by *E. coli* resistant to trimethoprim–sulfamethoxazole as well as other antibiotics. Concludes that UTIs may be caused by contaminated foods, as the outbreaks appear to follow a pattern similar to that of *E. coli* O157 as they spread throughout a community.

Fluoroquinolone resistance in *Camplyobacter* absent from isolates, Australia. L. Unicomb, J. Ferguson, T.V. Riley and P. Collignon. *Emerging Infectious Diseases,* 2003. 9(11): 1482-1483.

Summary: Reports on a study of fluoroquinolone resistance in New South Wales, Australia, over a three-year period. Only 12 *Campylobacter* isolates were found to be resistant to fluoroquinolones. Ten of these were related to travel; travel status of the other two is unknown. Australia has never allowed the use of fluoroquinolones in food animal production, a policy that may have impacts on human health for countries with fluoroquinolone-resistant cases of *Campylobacter*.

Possible animal origin of human-associated, multidrug-resistant, uropathogenic *Escherichia coli.* M. Ramchandi, et al. *Clinical Infectious Disease,* 2005. 40: 251-257.

Summary: Reviews a collection of 495 animal and environmental *E. coli* isolates collected by the Gastroenteric Disease Center and determines that 26 percent had indistinguishable characteristics from human isolates. Concludes that the data suggest that drug-resistant, uropathogenic, human-associated *E. coli* strains may have an animal origin and that drug-resistant urinary tract infections in humans could be derived from foodborne illnesses.

The rising influx of multidrug-resistant gram-negative bacilli into a tertiary care hospital. A.E. Pop-Vicas, E. M. C. D'Agata. *Clinical Infectious Diseases*, 2005. 40: 1792-8.

Summary: Studies multi-drug resistant (MDR) *E. coli*, *Klebsiella* species, *Enterobacter cloacae*, and *Pseudomonas aeruginosa* isolates from patients harboring these bacteria upon entering a hospital in Israel (within 48 hours of admittance). Finds that between 1998 and 2003 the prevalence of MDR isolates of all listed species increased significantly except *Pseudomonas aeruginosa.* Of the 464 isolates collected 12 percent, 35 percent and 53 percent were resistant to 5, 4 and 3 antimicrobial groups, respectively.

Analysis of a uropathogenic *Escherichia coli* clonal group by multilocus sequence typing. S.Y. Tartof, O.D. Solberg, A.R. Manges, L.W. Riley. *Journal of Clinical Microbiology*, 2005. 5860-5864.

Summary: Forty-five strains of uropathogenic *E. coli* were analyzed by a molecular typing method called multi-locus sequence typing (MLST). The research shows that one sample from a cow grouped with other human isolates collected from urinary tract infections and bacteremia . This shows that *E. coli* from animals may be a cause of UTIs and bactermia in humans.

Low-level fluoroquinolone resistance among *Camplyobacter jejuni* isolates in Australia. L. Unicomb, J. Ferguson, R.J. Stafford, R. Ashbolt, M.D. Kirk, N.G. Becker, M.S. Patel, G.G. Gilbert, M. Valcanis and L. Mickan. *Clinical Infectious Diseases,* 2006. 42: 1368-1374.

Summary: Reports a study from five Australian states between 2001 and 2002 that looked into the susceptibility patterns of *Campylobacter jejuni*. Only two percent of isolates from locally acquired infections were resistant to ciprofloxacin, likely reflecting Australia's policy of restricting the use of fluoroquinolones in food production animals.

First report of the emergence of CTX-M-type extended spectrum ß-Lactamases (ESBLs) as the predominant ESBL isolated in a U.S. health care system. J. S. Lewis II, M. Herrena, B. Wickes, J.E. Patterson, J. H. Jorgensen. Antimicrobial Agents and Chemotherapy, 2007. 51(11): 4015-4021.

Summary: A study on Extended spectrum beta-lactamases (ESBLs) from a clinic in San Antonio Texas. ESBLs are enzymes produced by bacteria that can negate the use of certain newer antibiotics used in treating infections of *E. coli* or similar bacteria. The new ESBL enzyme described here as seen for the first time in the U.S. is located on a plasmid (a mobile element of DNA) within the bacterium. As plasmids can be readily passed between bacteria this new finding could have a wide health impact. The authors state "a worrisome trend with the emergence of these enzymes has been an increasing frequency of *E. coli* isolates from outpatients or patients hospitalized for a very brief period, suggesting community acquisition of these strains."

Endemic and epidemic lineages of *Escherichia coli* that cause urinary tract infections. A.R. Manges, H. Tabor, P. Tellis, C. Vincent and P. Tellier. *Emerging Infectious Diseases,* 2008. 14(10): 1575-1583.

Summary: Studies urinary tract infections (UTI) in women from California and Canada. Relatedness of the infections is apparent, as the profiles of the bacteria are identical. Multidrug-resistant *E. coli* outbreaks are the causative agent of the disease, and how these bacteria are acquired by the gut is unclear; however, the authors cite a previous study indicating that poultry and pork consumption may lead to the development of drug-resistant UTIs.

Temporal changes in the prevalence of community-acquired antimicrobial-resistant urinary tract infection affected by *Escherichia coli* clonal group composition. S.P. Smith, A.R. Manges, L.W. Riley. Clinical Infectious Diseases, 2008. 46: 689-695.

Summary: Reports on urinary tract infections (UTIs) from 1,667 patients over the course of 6 years. *E. coli* specimens were collected and characterized by molecular methods. Twelve percent of human UTI samples collected were found to be from a specific group, which from previous work has been shown to include *E. coli* that had been collected from food animals or retail poultry products. The collected human isolates were also shown to be resistant to trimethoprim-sulfamethoxazole at a rate of 49 percent. The authors suggest that contaminated food products may be a source of drug resistant UTIs.

Hospital and societal costs of antimicrobial-resistant infections in a Chicago teaching hospital: Implications for antibiotic stewardship. R.R. Roberts, B. Hota, I. Ahmad, R.D. Scott II, S.D. Foster, F. Abbasi, S. Schabowski, L.M. Kampe, G.G. Ciavarella, M. Supino, J. Naples, R. Cordell, S.B. Levy and R.A. Weinstein. *Clinical Infectious Diseases,* 2009. 49: 1175-1184.

Summary: Assesses the attributable cost associated with antimicrobial-resistant infections (ARI). Data were collected from patients admitted to a public teaching hospital in the Chicago area in the year 2000. Of 188 patients that met eligibility of ARI, the attributable medical cost of

treatment ranged from $18,588 to $29,069 per patient. Social costs were $10.7 to $15.0 million, and total cost corrected to 2008 dollars was $13.35 million.

Antibiotic management of Staphylococcus aureus infections in US children's hospitals, 1999-2008. J.C. Herigon, A.L Hersh, J.S. Gerber, T.E. Zaoutis, J.G. Newland. *Pediatrics*, 2010. 125:e1294-e1300.

Summary: This study focuses on the rates of *S. aureus* infection in children under the age of 18 from 1999 until 2008. The authors also track the trend of antimicrobial use during that time period. Finds that *S. aureus* infections increased by a rate of more than 10-fold over the course of 10 years from 14.8 per 1000 admissions in 1999 to 35.7 per 1000 admissions in 2008. MRSA infections also increased 10-fold during the same period from 2.0 cases per 1000 admissions in 1999 to 20.7 cases per 1000 admissions in 2008. Increased use of clindamycin was most substantial (21 percent in 1999 to 63 percent in 2008) while linezolid also saw increased use between 2001 (when it became available) and 2008. The substantial use of clindamycin may lead to greater resistance and ineffective treatment of future *S. aureus* infections. The authors note that continuous monitoring of local *S. aureus* susceptibility patterns is needed as treatment patterns have changed over the past decade due to the emergence of community-associated MRSA.

Genetic identity of aminoglycoside-resistance genes in *Escherichia coli* isolates from human and animal sources. P. Ho, R.C. Wong, S.W. Lo, K. Chow, S.S. Wong, T. Que. *Journal of Medical Microbiology*, 2010. 59: 702-707.

Summary: A study in Hong Kong on *E. coli* isolates collected from food producing animals and humans (most from urinary tract infections). The group looked at the aminoglycocide (gentamicin) resistance characteristics of these isolates and found the main source of resistance was due to a gene called aacC2. The aacC2 gene was shown to exist in both human and animal *E. coli*. This suggests that gentamicin resistance in human *E. coli* urinary isolates can be attributed to resistance genes that are present in food-producing animals. Study illustrates when humans are in close contact with contaminated food, there is a risk of picking up antibiotic resistant *E. coli* that could lead to UTIs that are more difficult to treat.

Food reservoir for *Escherichia coli* causing urinary tract infections. C. Vincent, P. Boerlin, D. Daignault, C.M. Dozois, L. Dutil, C. Galanakis, R.J. Reid-Smith, P-P. Tellier, P.A. Tellis, K. Ziebell, A.R. Manges. Emerging Infectious Diseases, 2010. 16(1):88-95.

Summary: The design of this study was to see if a food reservoir exists for *E. coli* that may cause urinary tract infections. Sampling for *E. coli* was completed between 2005 and 2007 comprising clinical UTI samples, retail meats and restaurant/ready-to-eat foods. Upon comparison of these collected isolates by molecular methods the author's report that *E. coli* identified from retail chicken and other food sources are identical or nearly the same as those from human UTIs.

For additional information on the Pew Campaign on Human Health and Industrial Farming, or on any of these studies, please contact Laura Rogers, Project Director, Pew Health Group, at (202) 552-2018 or **lrogers@pewtrusts.org**.

Ms. SCHAKOWSKY. [Presiding] Thank you.
Dr. Hoang.

STATEMENT OF CHRISTINE HOANG

Dr. HOANG. Thank you for the opportunity to speak about antimicrobial resistance and the use of antimicrobials in animal agriculture. My name is Dr. Christine Hoang and I represent the American Veterinary Medical Association.

As a veterinarian with a dual degree in veterinary medicine and public health, and additionally certified in public health, my work is largely focused on scientific evaluations to inform the decision-making process both domestically and abroad through the AVMA, the Codex Alimentarius Commission and prior to that the Food and Agricultural Organization of the United Nations.

The AVMA's 80,000 members are engaged in every aspect of veterinary medicine and public health. As veterinarians, our oath ethically charges us with promoting public health and protecting animal health and welfare. With that also comes the responsibility to be cognizant of the potential health impacts in humans that may occur as a result of any decision that we make. The veterinarian must always the consider individual animal, other animals and humans in contact with that animal, and if it is a food animal, we must ultimately consider the people who consume the end product. The decisions of the veterinarian go far beyond a single animal or person and an entire herd or flock and potentially hundreds of thousands of people that are affected by the many foods that are produced by a single animal. Therefore, as veterinarians, we carry a heavy burden but we do willingly with the knowledge, education and ability to make the right decision and to use the tools that are available to us appropriately and judiciously. Our members share the same concerns as our human health counterparts but yet we have additional concerns that must be considered: impacts on animal health and welfare and even negative impacts on human health that are often unrealized.

Two decades ago, a study concluded that human health hazards from growth-promoting uses could not be proven nor disproven. The debate continues today for that very same reason. A direct epidemiologic investigation still cannot be completed. Furthermore, there are divergent opinions due to differing levels of acceptable risk. For example, a person might find risk associate with food unacceptable, any risk would be unacceptable, but risks associated with high-speed driving perfectly permissible.

As veterinarians, we must consider many risks, risk to the animal, risk to ourselves, risk to our clients, risk to public health, risk of action and risk of inaction, and the accepting of some of those risks in order to minimize others. Whenever antibiotics are used, there is some risk of resistance developing. That risk resistance can be transmitted to humans yet systems are in place that can trigger further investigation to determine the level of those associated risks. Risk analyses that evaluate only risk report adverse effects ranging anywhere from one in 32,000 to seven in 100 million. Risk analyses that also consider benefits indicate an increase in thousands of sensitive strained human cases for a reduction of a frac-

tion of a single resistant case. Therefore, the greater risk of foodborne illness must be weighed against the many other factors.

We caution against preemptive bans based on the following observations in other countries: significant increases in therapeutic use as a substitution for growth promoters. The need for increased therapeutic uses are indicative of a decline in animal health and welfare associated with disease and no clear evidence of a significant human health benefit. Veterinarians are trained medical professionals with the ability to predict disease conditions and recommend appropriate therapy. Those uses should not be considered injudicious nor banned as routine use. If a disease is predictable and can be prevented, it is incumbent upon the veterinarian to initiate appropriate therapy to prevent animal pain and suffering. Although over-the-counter antibiotic are available for such therapies, they are not unregulated. If a drug is not used according to the approved label indications for the dose, duration, disease or species or within extra-label drug use regulations, it is illegal.

The AVMA's antimicrobial use task force recently concluded that veterinarians should be involved in the decision-making process for the use of all antimicrobials in animals regardless of the distribution channel through which it was obtained. This would encompass prescription products, veterinary feed directives and over-the-counter antibiotics. Without exception, the AVMA is supportive of measures to mitigate risk to human health. To avoid potential diversion of resources away from more appropriate disease control measures, we encourage a regulatory strategy that is based on science, risk and benefit analysis, risk management that is commensurate with the level of risk, and cooperation with all relevant stakeholders. The AVMA is committed to providing consumers with the safest food possible and to protect human health against the current risk without compromising the health of food animals.

Thank you for the opportunity to appear before you today.

[The prepared statement of Dr. Hoang follows:]

TESTIMONY OF

Christine Hoang, DVM, MPH, CPH

Assistant Director

American Veterinary Medical Association

Concerning

Antibiotic Resistance and the Use of Antibiotics in Animal Agriculture

Before the U.S. House of Representatives,

Committee on Energy and Commerce,

Subcommittee on Health

July 14, 2010

Thank you, Mister Chairman and members of the Subcommittee on Health, for providing the American Veterinary Medical Association (AVMA) with the opportunity to speak about antimicrobial resistance and the use of antimicrobials in animal agriculture.

My name is Dr. Christine Hoang, and I am an Assistant Director in the Scientific Activities Division of the American Veterinary Medical Association. In addition to a doctorate in veterinary medicine, I also hold a master of public health degree with concentrations in veterinary public health policy, both national and international, as well as epidemiology[a] and am additionally certified in public health. My work focuses upon science based policy for food safety, zoonotic disease[b], and antimicrobial resistance on behalf of the veterinary profession. Not only are these topics of public interest, but these are topics that require a great deal of intensive research and careful evaluation.

Established in 1863, the AVMA is a not for profit association representing more than 80,000 U.S. veterinarians engaged in every aspect of veterinary medicine and public health – private and corporate practice, government, industry, academia, and uniformed services. As veterinarians, our oath ethically charges us with promoting public health and protecting animal health and welfare. With that also comes the responsibility to be cognizant of the potential human impacts that may occur as a result of any decision we make. When a veterinarian makes the decision to use a drug, any drug, especially in a food animal, that person must consider the individual animal; other animals that may come into contact with that animal; humans who may come into contact with that animal; and if it is a food animal, we must ultimately consider the people who consume the end product. In today's world, the decisions of a veterinarian affect far beyond a single animal or person – it is an entire herd or flock and potentially hundreds or thousands of people affected by the many foods that are produced from a single animal. Therefore, as veterinarians, we carry a heavy burden, but we do so willingly with the knowledge, education, and ability to make the right decisions and to use the tools that are available to us appropriately and judiciously. With respect to antimicrobial resistance, our members share the same concerns as our human health counterparts. Yet, we also have additional concerns that must be considered such as negative impacts on animal health and welfare or even negative impacts on human health that are often unrealized.

Risk – Benefit Assessments and Human Health Impact

Two decades ago, at the request of the Food and Drug Administration (FDA), a committee of the National Research Council was charged with evaluating the effects of penicillin, chlortetracycline, and oxytetracyline at levels for growth promotion or disease prevention on human health. The committee concluded that human health hazards could not be proven or disproven because it is impossible to determine antimicrobial exposures of individual animal sources of meat products[1]. The debate continues today for the very same reason. While there have been technological advances such as DNA fingerprinting that can identify clonal isolates, a direct epidemiologic investigation still cannot be completed. Therefore, antimicrobial resistance and the role of animal agriculture continue to be debated.

As the debate continues, it is important to understand that much of the varying opinions is due to differing levels of acceptable risks. For example, as an individual, a person may not accept any risks associated with food and yet be extremely tolerant of risks associated with driving at high speeds. As veterinarians, we must consider many risks – risks to the animal, risks to ourselves, risks to our clients, risks to public health, risks of action, and risks of inaction – and be accepting of some of those risks in order to minimize other risks.

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[a] Epidemiology is a medical discipline that is the study of the causes, distribution, and control of disease in populations and serves as the foundation and logic of interventions made in the interest of public health and preventive medicine.

[b] Zoonotic diseases are diseases that can be transmitted from animals to humans. CDC estimates at least 60 percent of all human diseases and 75 percent of all newly emerging diseases are zoonotic.

Whenever antimicrobials are used, there is some risk of resistance developing. Therefore, similar to human medicine, clinical infections do occur and resistance in food animals does develop. That resistance can be transmitted to humans, however multiple monitoring and surveillance systems are in place that can recognize impactful events and trigger further investigation to determine the level of associated risks. One of those systems is the FDA adverse event reporting system which should include treatment failure as a result of resistance. Another system is the National Antimicrobial Resistance Monitoring System (NARMS) that monitors resistance in foodborne human enteric pathogens as well as resistance in animals. The retail meat NARMS surveys and the animal arm of NARMS, provide a more comprehensive view of antimicrobial sub-populations than the NARMS human data that are collected. Furthermore, resistance is closely monitored through diagnostic samples and retail meats with an overrepresentation in sampling. The NARMS sample collection design ensures that resistant animal isolates are overrepresented.

Recognizing that food is the most likely route of transmission of resistance from food animals to humans[2], the AVMA supports the use of multidisciplinary and multi-hurdle[a] approaches[3] to safeguard our food supply and minimize the potential for any adverse impacts on human health. For instance, on the farm, we encourage the continued improvement of animal husbandry and management practices, the development of new technologies to advance animal health, and the continued availability and judicious use of antimicrobials. Post-harvest, we support the on-going improvements of Hazards Analysis and Critical Control Points (HACCP) based pathogen reduction programs – all of which to ensure a safe, healthy, and wholesome food supply. Some data suggest post harvest interventions, such as hyperthermia and disinfection can influence the survival of resistant bacteria, and should be further investigated.[4]

To minimize risks to human health, the FDA requires antimicrobial manufacturers to provide information to show that a proposed animal drug will not harm public health. The procedure ensures zero-risk for human safety because drugs that pose risks beyond "a reasonable certainty of no harm" to human health are rejected or the use of the antimicrobial may be limited in order to mitigate the adverse effect. Antimicrobials approved since the implementation of the FDA Guidance for Industry #152 (a risk analysis process) in 2003, have undergone a comprehensive, evidence-based approach to prevent the emergence and selection of antimicrobial resistant bacteria that may adversely affect human health. Because the extent-of-use limitations table in GFI #152 assigns a high ranking for intended administration to flocks or herds of animals, it is extremely difficult or impossible for FDA to approve antibiotics for use in feed or water for treatment of groups of animals, if those same antibiotics are also used in humans. Unfortunately, few new antimicrobials are currently being developed. While several drugs are developed and reserved for human use, only one new drug (tiamulin) has been made available for treating animal disease in recent years. Therefore, the antimicrobials that were approved decades ago (and in the same classes as some human use antimicrobials) may be the only antimicrobials available for use in herds and flocks to combat infectious diseases and safeguard the food supply.

Given the pre-approval safety measures taken by FDA, further action to restrict antimicrobial use in animals should only occur if there is an imminent threat to human health or if the data clearly show that there is a threat developing following an accurate scientific risk assessment. The risk assessment must be conducted to facilitate risk-based decisions concerning the appropriate and judicious use of antimicrobials. Risk analyses should continue to evaluate the risks and benefits to animal health and welfare, in addition to the risks and benefits to human health attributed to uses in food animals. Risk analyses include risk assessment, risk communication, and risk management actions that are commensurate with the level of risk that is determined through risk assessment. Following a risk assessment, the risk management action may simply be to allow continued availability of the product with no changes because the level of risk has been determined to be insignificant, or the action may be to withdraw approval of the drug product. Other actions by the FDA can also include review by the

[a] The multi-hurdle concept refers to the interaction of factors that affect microbial behavior in foods. Under some circumstances these effects are additive. Under others, the implication is that synergistic interactions lead to a combined effect of greater magnitude than the sum of constraints applied individually.

Veterinary Medicine Advisory Committee or limitations of use such as use only for certain indications.

Several antimicrobial risk assessments have been performed demonstrating varying risks to humans depending on the drug and the specific use of the drug. This further emphasizes the need to ensure science based risk assessments on a drug by drug basis to fully inform the regulatory process. One of FDA's risk assessments concluded that an unacceptable level of risk (1 in 34,945 people estimated to be affected in 1998 and 1 in 32,912 in 1999) for flouroquinolone resistant *Campylobacter* as a result of poultry consumption due to the use of enrofloxacin in poultry[5] resulting in withdrawal of the product in 2005. Yet, the desired outcome of minimizing fluoroquinolone resistant *Campylobacter* in humans remains questionable as human cases continue to rise[6].

Another risk assessment by FDA in 2004[7] could not form conclusions as to whether the use of streptogramins (virginiamycin, an antimicrobial growth promoter) in food animals contributes to the occurrence of streptogramin-resistant *E. faecium* (SREF) infections in humans via a foodborne pathway. In fact, the FDA found the different Minimum Inhibitory Concentration (MIC) distribution and the dissimilar pattern of resistance genes between animal and human isolates to be inconsistent with an attribution of human streptogramin resistance to animal sources, meaning the resistance did not come from an animal source. Regardless, if it were to occur, the average risk to a random member of the US population of having SREF and impaired Synercid® (a streptogramin used to treat bacterial infections in humans) therapy as a result of animal uses of virginiamycin ranges from 7 in 1 billion to 14 in 100 million per year. In Denmark, where virginiamycin has been banned since 1998, resistance to Synercid® is much greater than what is seen in the US.[8]

In 1987, at the request of the FDA, an Institute of Medicine study was conducted to evaluate the risks associated with penicillin and tetracyclines at growth promotion and prevention levels. The study estimated approximately 6 deaths per year attributable to the use of penicillin and/or tetracyclines for growth promotion and disease prevention. When only used for growth promotion, that number decreased to 2 deaths per year.[9] When compared to estimated risks from the use of enrofloxacin for treatment[10], this data is contrary to the assumption that growth promotion uses are inherently stronger drivers of resistance than treatment uses and therefore cause human health hazards.

Other risk assessments also demonstrate a very low risk to human health from the use of antimicrobials in food animals. With an approximate probability of less than 1 in 10 million per year for macrolide resistant *Campylobacter* infections and approximately 1 in 3 billion for *E. faecium* infections, a unique farm-to-patient risk assessment demonstrates that the use of tylosin and tilmicosin (macrolides) in food animals presents a very low risk of human treatment failure.[11]

Another risk assessment examines the impact of the use of penicillin-based drugs in food animals on penicillin/ aminopenicillin resistant enterococcal infections. The conclusion indicated that no more than 0.04 - 0.18 excess mortalities per year would be prevented in the entire U.S. population by discontinuing current use of penicillin-based drugs in food animals. The true risk could be as low as zero.[12] This equates to one potentially preventable mortality in the U.S. population approximately every 7-25 years. Similarly, another risk assessment concluded that veterinary use of macrolides in Danish pigs resulted in a low risk to human health.[13]

Some of the models using a risks and benefits model predict an increased human health burden if the use is withdrawn. Utilizing that model, a risk assessment for virginiamycin evaluated benefits to humans in addition to the risks. That assessment found an increase of 0.27 cases per year of streptogramin-resistant and vancomycin-resistant *E. faecium* (VREF) potentially resulting from the use of virginiamycin. Yet, as a benefit of continued use, the assessment found a significant increased human health risk if virginiamycin use is withdrawn – an additional 6,660 cases of campylobacteriosis per year. The benefit of continued use and preventing those additional 6,660 cases per year of campylobacteriosis would far outweigh the minimal risks of an increased 0.27 cases per year of streptogramin-resistant and vancomycin-resistant *E. faecium* (VREF).[14] Another risks and benefits assessment concluded that withdrawal of macrolide and fluoroquinolone use is estimated to cause significantly more illness days than

it would prevent.[15]

Others have estimated that risk management strategies focusing on eliminating resistance are expected to create < 1% of the public health benefit of strategies that focus on reducing microbial loads in animals or on foods.[16] We must consider this information within the context of food safety, animal health and welfare benefits that are gained by focusing on pathogen reduction strategies, including judicious antimicrobial use. Another study agrees, concluding that, "antimicrobials that benefit animal health may benefit human health, while regulatory interventions that seek to reduce antimicrobial resistance in animals may unintentionally increase illness rates (and hence antimicrobial use and resistance rates) in humans..."[17]

Information derived from studies of organic or antibiotic-free production practices compared to traditional production practices is inconclusive, but there are indications that organically grown meat may have less-resistant organisms but greater prevalence and quantities of pathogens on the meat.[18,19,20,21] Therefore, the greater risk of foodborne illness derived from these products must be weighed against the many other factors such as the likelihood of treatment failure if treatment is necessary.

The question of what the nature and magnitude of the risk to humans is can only be answered by performing systematic risk assessments. Such risk assessments must include identification of the endpoints of concern (e.g., increased illness or mortality caused by bacteria resistant to antibiotics used to treat the disease in humans), the nature of the treatment protocols in food animals, the potential routes of exposure, characterization of the population at risk, and the probability of occurrence. Furthermore, risk assessments that also consider benefits will provide a more balanced perspective and fully inform the decision making process.

Antibiotics as a tool to prevent and control disease in animals and humans

The use of drugs in animals is fundamental to animal health and well-being. Of the tools that are available to veterinarians, one of the most important tools that veterinarians use to protect human health and animal health is the judicious use of antimicrobials. Antibiotics are necessary to relieve pain and suffering associated with disease conditions in animals. For food animals, drugs additionally contribute to the public health by mitigating disease and thereby reducing the numbers of bacteria entering the food supply. Studies show that a reduction in the incidence of food animal illness will reduce bacterial contamination on meat, thereby reducing the risk of human illness.[22,23,24,25,26,27,28,29] The continued availability of safe, effective antimicrobials for veterinary medicine, including the retention of currently approved drugs and future approvals of new drugs, are critical components of ensuring a safe food supply and essential to the improvement of animal health and welfare.

Just as in humans, resistant bacteria can and do develop in animals. However, many of the important details regarding the transfer of that resistant bacteria, or even resistance genes – to the environment or humans – still remains in question. Simply because resistance exists in animals, it does not necessarily equate to a significant human health risk. First, the bacteria or its resistance determinants may not effectively transfer to humans through the food chain. Secondly, the resistant pathogen may not colonize in humans to create disease. Third, if a disease does occur, antimicrobial therapy may not be indicated, and the disease resulting from the resistant bacteria is in effect no different than any other bacteria. In the vast majority of cases, antimicrobial therapy is not needed. Supportive therapy, such as fluids, is the only treatment that is needed for most *Salmonella*, *Campylobacter* and *E. coli* infections. For non-typhi *Salmonella,* antimicrobial therapy is generally not indicated because it has no effect on clinical illness and prolongs carriage and excretion of the organism. For *Campylobacter jejuni*, antimicrobial therapy is unlikely to provide benefit. Treatment of enterohemorrhagic *E. coli* (*E. Coli O157*) may increase the risk of developing hemolytic uremic syndrome.[30] Lastly, if antimicrobial therapy is needed, even if the pathogen is resistant to one drug or multiple drugs, it may be still be susceptible to the drug of choice.

Routes of Transmission

There are several theorized mechanisms for the spread of resistance from animals to humans: 1) Via residues 2) Direct route - when an individual consumes resistant bacterium in food or by direct contact with an animal infected with a resistant organism 3) Indirect route - through a resistance reservoir where an individual acquires a resistance determinant from that resistance reservoir (the animal food product).

Residues

There is an extremely low risk of developing resistance as a result of antibiotic residues. Furthermore, that risk only exists if there are a series of flaws in the system that has been designed to protect the public from drug residues in food products. Whenever drugs are used to treat sick animals or prevent disease or when animals are exposed to chemicals in the environment, there is the potential for remnants to remain in the meat or other animal products (often known as residues). The FDA establishes tolerances for drug residues to insure food safety. The FDA also establishes "withdrawal times" or "withholding periods" which are times after drug treatment when milk and eggs are not to be used for food, and during which animals are not to be slaughtered. This allows time for the animals to metabolize and eliminate the drugs that had been used for treatment.

Maximum residue limits and tolerances for drug residues protect us from residues that may impact human health. If withdrawal times determined by the FDA are insufficient or are not adhered to, then there is the potential for violative residues. Also, if the tolerance levels are inadequate or ineffectively enforced, then again there is a possibility for a human health hazard. However, in addition to those systematic errors, two additional conditions must be met for the residue to pose a risk for the development of resistance: the drug residue must retain its efficacy through processing and/or cooking and remain as an active compound to affect human gut flora; and the drug residue remaining must be of a sufficient level to select for resistance in humans.

Direct Route

The direct route of transmission is also based on a series of events. There are many ways in which an animal can be infected with a resistant bacterium. Quantity of use is not necessarily the sole factor in selecting for resistance, nor is the dose or a particular purpose for antimicrobial use. Also of note, the use of a particular drug is not necessarily the cause of resistance to that same drug. The process of co-selection remains unclear and there is an increasing amount of evidence that resistance acquisition mechanisms are far more complex than previously thought. Resistance is mediated by certain genes and for many genes it is still unclear what causes the resistance gene expression or even development. Therefore, it is important to recognize that the use of a drug itself should not be a focus or rationale for restrictions on antimicrobials, but rather factual outcomes that are far more informative must be considered.

If an animal is infected with resistant bacteria at the time of slaughter and the carcass remains contaminated with the resistant bacteria through slaughter and processing, a sufficient microbial pathogen load must remain after processing and post harvest interventions (such as carcass rinses) to pose a threat to human health. The pathogen must then survive cooking in sufficient quantity to cause infection, or proper food hygiene procedures not followed. An individual must consume the contaminated food, become ill, seek medical attention, and in the worst case scenario, there is treatment failure as a result of the resistant pathogen. In most cases, medical attention is not sought and antimicrobial treatment is contraindicated.

As an example providing a comparative perspective on risk through a direct route of resistance transmission, a study on fluoroquinolone use in beef cattle had estimated the likelihood of a fluoroquinolone resistant *Campylobacter jejuni* infection causing a human death to be approximately a 1-in-250 million assuming the person had acquired the infection by eating contaminated ground beef.[31] In

comparison with this risk that may be associated with the consumption of contaminated beef, a person is 567 times more likely to be killed in a plane crash and 14,284 times more likely to be killed in a car crash in any given year.[32]

Indirect Route

The indirect route of transmission is theoretical, shown to be possible experimentally in vitro with no clear indication of what will occur in vivo. This route consists of many assumptions and a series of required events before a risk to human health can occur as a result of antimicrobial use in food producing animals. Resistance determinants are presumed to be present in a food producing animal as the resistance reservoir. Then the determinants must follow the same pathway as the direct route of transmission through the food chain: The animal food product must be contaminated with the determinant during slaughter; the determinant survives processing and cooking; is effectively transferred to an organism in the human; the human pathogen expresses the gene or passes it to yet another organism until there is gene expression; the organism causes human illness; the person seeks and needs medical attention; and in the worse case scenario, the person experiences treatment failure as a result of the resistance.

An example of the indirect route of transmission and concept of resistance reservoirs can be illustrated through the extended spectrum beta-lactamases (ESBLs). The concept of resistance reservoirs suggests that a pool of resistance genes is maintained within certain environments and poses a risk to public health. Scientists have detected similar, but not identical ESBL genes in both humans and animals in an isolated geographic region.[33] In Denmark, the initial cases of ESBL resistance had been detected in imported animals and food products prior to 2003. In 2005 and after, ESBL producing organisms were detected in domestic animals and animal products. In 2007, Denmark experienced the first major human outbreak with ESBLs. One interpretation of this series of events has been the application of the resistance reservoir concept. Based on the temporal sequence of events, many have theorized that animals, particularly those raised outside of Denmark with less stringent antimicrobial controls in animal agriculture, are serving as a reservoir for the ESBL resistance genes and transferring those mechanisms of resistance through the food chain. An alternative theory could suggest that ESBLs in animals and animal products have evolved and spread due to increased therapeutic antimicrobial use after the bans on growth-promoting antibiotics. Much of the increased use in animal agriculture has more often been in the same classes as human use antimicrobials and at greater doses. Since 1998, the consumption of β-lactams in food producing animals in Denmark has nearly doubled. Likewise, the development and spread of ESBL resistance genes in humans may be due to increased antimicrobial use in human medicine. Since 1998, human consumption of β-lactams in Denmark has nearly quadrupled. Some experts speculate that this increase in human use may be due to shortened hospital stays and increased perioperative prophylactic use.[34] Thus, it is plausible that ESBLs are transmitted through the food chain, but the probability, frequency, and efficiency of that transfer remains unknown.

Not all antimicrobials or all their uses are equal in their probability of developing resistance or creating a risk to human health, further elucidating the need for individual risk assessments. Based upon risk assessments conducted and epidemiological evidence obtained thus far, the risk to people of resistant infections from consuming animal products appears to be very low, as the use of antimicrobials in animals is only one of the many factors that can impact antimicrobial efficacy in treating these infections. In terms of animal agriculture, the main goal of mitigating risks to human health should be to decrease the spread of foodborne pathogens, rather than focusing upon what is presumed to be the source of antimicrobial resistance. Moreover, prior attempts to decrease use of antimicrobials in animals in other countries have not been shown to significantly decrease resistant infections in people. Thus, broad-based bans and other limitations on antimicrobial treatments in food animals cannot be expected to produce the desired result of enhancing human health. In addition, many antimicrobials used in food animals have no medically important counterpart in human medicine, so the concept of reducing these uses bears no impact at all on human infections.

AVMA's Efforts

The AVMA has maintained three primary objectives when considering antimicrobial use:

1. Safeguarding public health,

2. Safeguarding animal health, and the

3. Continued availability of effective therapeutic agents, including antimicrobials for veterinary medicine and the retention of currently approved, safe drugs and biologics as well as future approvals of new therapeutic agents.

The veterinary profession strives to promote optimal human health and public health through zoonotic disease prevention and control, which includes foodborne pathogens among other diseases. To achieve optimal animal health as well as animal welfare, and in turn, human health, the veterinary profession must practice the same fundamental principles of public heath – prevention and control of disease in food animal medicine and population medicine[a]. While the end goal is the same for all medical professionals – good health – veterinarians are severely limited in our tools for disease control and prevention. Regulations for drug approvals are more stringent for food animal drugs than human drugs, therapeutic agents can be more difficult to develop, and there are fewer treatments available. Thus, veterinarians must rely on their knowledge of clinical medicine to determine the best course of treatment. Given the numbers of food animal species, in addition to the diversity of disease conditions that affect animals, a relative scarcity of labeled indications accompanying FDA approved drugs exists. Although the FDA, the AVMA and others have made and continue to make significant strides in enhancing drug availability, including legislative initiatives (such as the Minor Use and Minor Species Act, and the Animal Drug Availability Act), the numbers of FDA approved drugs are inadequate to meet veterinary medical needs, placing both animal health and welfare – and, potentially, human health – at significant risk.

Other successes through collaborative efforts include a decline in foodborne illness from meat and poultry products[35] as well as a decline in the prevalence of foodborne pathogens (including Salmonella) associated with meat and poultry[36] and resistance of those organisms[37]. These are all a result of improvements in animal health and the joint efforts of stakeholders.

The AVMA has also advocated for more research to support scientifically based therapeutic practices, such as epidemiological studies, that assess the effects of antimicrobial use. We support the scientifically valid and meaningful collection and review of data for all uses of antimicrobials and other pharmaceuticals used in humans and animals. We urge that such data be collected in concert with other data necessary to explain or inform fluctuations in use, e.g., disease prevalence, regional data, populations of animals, etc. An example is the USDA program, Collaboration for Animal Health, Food Safety and Epidemiology, that is attempting to study the use of antimicrobials on farms correlated with disease occurrence, and the effects of antimicrobial use on antimicrobial resistance as measured both on the farm and during processing of the meat from the specific farm. The AVMA also provided start-up funding for projects to create a nationally coordinated laboratory system to test for and report on resistance in animal pathogens and to create a decision support system to assist veterinarians when making antimicrobial use decisions. Unfortunately, while this project received follow-on funding by the FDA, it has not been sustained or completed.

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[a] Population medicine is a medical discipline focusing on the concepts of public health and epidemiology. In veterinary medicine, these concepts are incorporated to make strategic decisions to advance animal and herd health.

Veterinary Oversight, Judicious Use, and VCPRs

Since 1998, the AVMA has actively worked to mitigate the development of antimicrobial resistance related to the use of antimicrobials in food animals. The AVMA Guidelines for the Judicious Therapeutic Use of Antimicrobials were developed to safeguard public health by providing specific recommendations for responsible and prudent therapeutic use of antimicrobials. With support and input from the CDC, Infectious Diseases Society of America, the FDA, and the USDA, the guidelines were developed in collaboration with our species specific allied veterinary organizations. These guidelines were based upon carefully reviewed, scientifically sound research, and we believe that our members conscientiously adhere to the principles of judicious therapeutic use of antimicrobials to ensure the protection of human health, as well as animal health and welfare.

We have actively encouraged and assisted our allied veterinary organizations to use the AVMA general principles as a template to develop more detailed guidelines appropriate to each species, disease and type of client. The AVMA also worked with these groups to develop and deliver a continuing education program to raise awareness within the profession and to encourage utilization of the principles. Fundamentally, the guidelines encourage scientifically based therapeutic practices, the use of antimicrobials only when needed, and compliance with all existing regulatory requirements when antimicrobials are used. For example, the American Association of Avian Pathologists (AAAP) Guidelines to Judicious Therapeutic Use of Antimicrobials in Poultry states, "Antimicrobials in Class III used at labeled instructions should be considered first if farm history, in vitro sensitivity and clinical judgment warrants." In the AAAP guidelines, Class III antimicrobials are identified individually and noted to be those of no or minimal importance to human medicine. The guideline further outlines disease specific diagnostics, non-antimicrobial interventions, and suggested antimicrobial interventions as a last resort.

Much of the discussion on antimicrobial use in animal agriculture revolves around a category commonly known as growth promotion or a group of antimicrobial uses that are poorly categorized as "non-therapeutic" or "sub therapeutic." The terms "non-therapeutic," and "sub-therapeutic," have no consistent definition. The use of ill-defined or inconsistent definitions only serves to further confuse the issue. We caution against indiscriminate use of these terms. Alternatively, we advocate using the definitions of the Codex Alimentarius Commission (an organization of the World Health Organization and the Food and Agricultural Organization of the United Nations), the FDA, and AVMA. All three organizations classify treatment, prevention, and control of disease as therapeutic uses. Antimicrobials that are labeled for production uses such as increased rate of gain or feed efficiency are often referred to as growth promoters.

Additionally, it is important to recognize that veterinarians are the trained professionals who know when antimicrobials are indicated in animals and when they are not. While some production systems can provide benefits in meeting an animal's behavioral needs, the costs can often be an increase in risk of disease.[38] Even in pristine conditions, at certain life stages, and under certain stressful circumstances, disease outbreaks can be predictable. In some of these cases, a veterinarian may choose to recommend the use of antimicrobials during those predictable stages to strategically prevent or control disease. The ability of a trained medical professional to predict a disease outbreak and recommend appropriate therapy should not be considered injudicious nor banned as "routine use."

There is little debate on the use of antimicrobials for treatment of disease in animals showing obvious clinical signs. However, few understand the importance of disease control and prevention, and even fewer have a clear understanding of growth promotants. Prevention and control of disease are key elements in the practice of veterinary medicine, particularly in animal agriculture, where the focus is on population health. This concept of disease prevention and control through herd health is analogous to public health efforts. If a disease is predictable and can be prevented, it is prudent for the veterinarian to recommend therapy to prevent animal pain and suffering that would occur associated with the disease condition. Likewise, if an infectious disease condition has been established in a herd or flock, it is incumbent upon the veterinarian to initiate appropriate therapy to minimize further disease spread and alleviate associated pain and suffering. Additionally, some of the growth promoting antimicrobials have

no human health equivalent and thus no human health impact. In fact, studies show a potential health benefit from the use of growth promoting antimicrobials.[39,40,41,42,43,44,45,46]

While it may seem intuitive to some that healthy animals are critically important for safe food, there are few who understand the intricacies of why. As an example, it is fairly intuitive that an effective antibiotic will help decrease the bacterial load in food. What many do not understand is that it is extremely difficult to ascertain whether or not a particular animal is carrying certain bacteria. Animals can harbor types of bacteria in their intestinal tracts that have no effect on their health, but can cause illness in humans. Many bacteria such as *Salmonella*, are shed intermittently, can increase with physical stressors such as underlying infections, and cannot be easily detected by routine testing procedures. Thus, we must rely on the combination of many different types of interventions to protect our food supply. These interventions would range from prevention and control of disease before it occurs in animals, to post harvest interventions such as carcass rinsing to further minimize bacterial contamination in food.

Another concept that is often misunderstood or overlooked is how a seemingly unrelated illness, such as respiratory disease in a food animal, can affect the presence of enteric bacterial pathogens in the meat and therefore food safety. The example of air sacculitis, a respiratory disease that affects poultry, illustrates how food can be safer by treating an animal that does not exhibit obvious symptoms. Air sacculitis is a fairly common disease that can spread rapidly and often go undetected until slaughter. The disease causes tissues to become more friable[a] and difficult to remove during food processing. The increased handling and difficulty in processing increases the potential for damaging the intestines and contaminating the carcass with enteric pathogens that can be harmful to humans[47]. By controlling this disease through the use of antibiotics and/or other therapeutic agents, veterinarians assist producers in maintaining a healthy flock and a safe food supply. This example further illustrates the necessity to continually maintain and improve animal health in the preservation of food safety.

The AVMA also strongly encourages a veterinarian-client-patient relationship (VCPR) and veterinary consultation when implementing any treatment regimen. Dispensing or prescribing a prescription product (including antimicrobials) requires a VCPR. The VCPR is the basis for interaction among veterinarians, their clients, and their patients.

The veterinarian must have sufficient knowledge of the animal(s) to initiate at least a general or preliminary diagnosis of the medical condition of the animal(s). This means that the veterinarian has recently seen and is personally acquainted with the keeping and care of the animal(s) by virtue of an examination of the animal(s), or by medically appropriate and timely visits to the premises where the animal(s) are kept.

Veterinarians making treatment decisions must use sound clinical judgment and current medical information and must be in compliance with federal, state, and local laws and regulations. The veterinarian must also include consideration of: judicious use principles; food safety and public health; and producer education as a part of the treatment plan. After considerations have been made for animal, human, and the environmental health impact, veterinary authorization is required prior to dispensing of the prescription product.

There are older antimicrobials that are available in medicated feeds (over-the-counter or OTC drugs) that can be purchased without a veterinary prescription. However, this is not to say that these drugs are unregulated. In fact, there are greater restrictions on the use of antibiotics in animals than there are in humans. Feed mills that distribute medicated feeds are licensed to do so by the FDA. All FDA approved drug products are restricted to a very specific use, dose, and duration as indicated on the label. Veterinarians are strictly prohibited from using certain drugs in food animals. Veterinarians are also restricted by Extra Label Drug Use (ELDU) regulations. Therefore, if a drug is not used according to the label and FDA approved instructions or ELDU regulations, then it is illegal.

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[a] Friable is a term used in pathology to describe tissues that are brittle, fragile, and easily damaged.

To our knowledge, no new classes of antimicrobials have been approved by the FDA as an OTC drug since the 1980s. A newer category of drugs, the Veterinary Feed Directive (VFD) Drug category, was created by the Animal Drug Availability Act of 1996 to provide veterinary control for certain animal pharmaceuticals for use in feed that are not suitable for OTC status. Any animal feed bearing or containing a VFD drug shall be fed to animals only by or upon a lawful VFD issued by a licensed veterinarian in the course of the veterinarian's professional practice.

The AVMA recently convened the Antimicrobial Use Task Force to evaluate the veterinarians' role in all uses of antimicrobials. The Task Force concluded that veterinarians should be involved in the decision making process for the use of all antimicrobials in animals regardless of the distribution channel through which it was obtained. This would encompass prescription products, VFDs, and OTC antimicrobials.

In our unique role as the only profession that routinely operates at the interface of human and animal health, veterinarians must balance the need for animal health and welfare with the need of human health. Without exception, the AVMA is supportive of measures to mitigate risks to human health. Yet, we must emphasize the importance of science based risk analyses and risk management that is commensurate with the level of risk. Risk management measures can include any of the following: advisory committee review of an existing approval or application for a new animal drug approval; post-approval monitoring through systems such as the National Antimicrobial Resistance Monitoring System (NARMS); limitations on the extent of use (e.g., individual animals only for short duration of use); limited or broad extra-label use restrictions in some cases or all cases; and, finally, non-approval or withdrawal of a previously approved antimicrobial.

Although there are critical shortages in the veterinary workforce, particularly in food supply veterinary medicine and veterinary public health, veterinarians provide oversight and advice on the use of medications, including OTC antimicrobials, on a significant percentage of animal operations. *Feedlot '99* reports that all large operations and nearly all (96.5%) small operations used the services of a veterinarian. Large operations were more likely to use a veterinarian that made routine visits or employ a full-time veterinarian on staff than small operations. Conversely, small operations were more likely to use a veterinarian when the need for one arose. Veterinarian recommendations had strong or moderate influence on selection of an antimicrobial for nearly 100% of feedlots. Laboratory test results influenced 58.8% of feedlots strongly or moderately. Veterinarian recommendations and laboratory test results were more likely to strongly influence selection of antimicrobials on large feedlots than small feedlots. Almost three out of four feedlots provided formal training in areas related to antimicrobial use.[48]

The *USDA Swine 2006* reports approximately seven of 10 sites (69.1%) used a veterinarian during the previous year. A higher percentage of large and medium sites (88.1 and 85.0%, respectively) used a veterinarian during the previous year compared to small sites (60.8%). Nearly 5 of 10 large sites (46.8%) used an on-staff veterinarian. A similar percentage of large sites (42.5%) used a local practitioner. Overall, approximately half of the sites (49.5%) used a local veterinarian during the previous 12 months. About one of four sites (24.7%) was visited by a veterinarian five or more times. Producers used the services of a veterinarian for many purposes during the previous 12 months. A higher percentage of large sites used a veterinarian for blood testing, production record analysis, employee education, and quality assurance compared to small sites. For sites that had at least one veterinary visit during the previous 12 months, the highest percentage of sites used a veterinarian to treat individual pigs (63.8%) and to provide drugs or vaccines (62.6%). These are followed by vaccination consultation (48.6%), quality assurance (47.9%), blood testing (47.6%), nutritional consultation (19.8%), environmental consultation (19.0%), and employee training/education (18.0%).[49]

We believe that these numbers can be improved through the resolution of the critical shortage of the veterinary workforce by identifying resources and developing solutions in collaboration with key stakeholders to ensure that veterinary needs are met. Further studies and proposals should appropriately address the availability of veterinary services.

Data Collection and Review; Monitoring and Surveillance Systems

The AVMA believes that there is a critical need for improved, more robust monitoring and feedback systems for foodborne disease and antimicrobial resistance such as FoodNet and National Antimicrobial Resistance Monitoring System (NARMS). Since the mid-1990s, the FDA has coordinated the NARMS in cooperation with the CDC and the USDA. NARMS is a multi-agency program that includes monitoring for resistant bacteria in retail meats by the FDA, monitoring for resistant foodborne pathogens in humans by the CDC, and monitoring for resistant bacteria in animals on farms and animal products in slaughter and processing facilities by the USDA. The Foodborne Diseases Active Surveillance Network (FoodNet) is a collaborative project of the CDC, 10 states, the USDA, and the FDA to monitor trends of foodborne illness and attribute the illness to specific foods and settings. Veterinarians in both public and private practice actively participate in these national programs and AVMA has consistently advocated for funding to maintain and continually improve all of these programs.

We are pleased that in recent years reporting by NARMS has been timelier. Yet, we still find gaps in data collection, lack of clarity in the interpretation of trends, and uncertainty as to how the data may be used to determine action. We also note that there remains a disconnect between data collection systems. For example, FoodNet provides data on foodborne infections, including resistant bacterial infections, but does not specify the proportion or incidence of resistant foodborne illness. In fact, only 2 outbreaks of resistant foodborne bacteria have been reported in the past decade. One of which was as a result of raw milk cheese consumption. Yet, NARMS data incongruously provides resistance trends and specifies a relative proportion of resistant bacteria but does not indicate how or if it may relate to food and human infections. Therefore, there is a clear dissociation between resistant foodborne infections and the source. Lastly, and most importantly, there is no system for monitoring how or how much antimicrobials are being used in humans or animals. Without this critical piece of information, it is impossible to understand how various uses can impact the resistance trends.

The Netherlands

The MARAN 2008 report indicates an increase in total antibiotic use from 1998-2008. Part of the increase is attributed to an increase in therapeutic use as a substitution for growth promoters. Therapeutic use has doubled in 2007 when compared to 1999. Although therapeutic use in 2008 has declined compared to 2007, the report indicates the reduction is due to veterinarians stockpiling drugs at the end of 2007[50], a puzzling explanation that questions why the stockpiling occurred and the potential impact on data interpretation. Important data reported from MARAN indicates:

- Increase in ciprofloxacin resistant *Salmonella* infections in humans in 2008 compared to 2006/2007 with resistance to attributed to DT104. The source of increased incidence is unknown but not a Dutch animal source.
- Fluoroquinolone resistant *Campylobacter* continued to increase in humans and animals in 2008
- Resistance rates in *E. coli* continue to increase in pigs, broiler chickens, and dairy cows
- Resistance levels of *Enterococcus* remain high or increases in all animal species

This data would suggest that the ban of antibiotic growth promoters in the Netherlands has not achieved a decrease in total use, a decrease in therapeutic use, or a decrease in resistance levels.

Danish Experience

The Danish experience has taught us that there can be serious negative consequences in animal health and welfare following the withdrawal of growth promoting antimicrobials and few, if any, improvements or positive human health impact.

In the late 1990s, Denmark instituted a voluntary ban on the use of antimicrobials for growth promotion (AGPs). A complete ban of AGPs was initiated in 2000 and completed by the start of 2002. The following has been observed as a result of the ban on the use of antibiotics for growth promotion in Denmark:

In animals –

- From 2001 to 2008, the overall consumption of antimicrobials in pigs increased by 19%.
  - Consumption of tetracyclines increased by 118% per pig from 2003-2008.
- Consumption of all antimicrobials in food animals has gradually increased 110% from 1998-2008, while the meat production has increased 32%.[a]
- There has been increased death and disease in the swine herds, especially at the weaning stage (information inferred from DANMAP 2005 and other reports on pigs). According to published news reports, there was a relative increase of 25% in the number of pigs that died from illnesses from 1995 to 2005.
- Nearly double the quantity of antimicrobials is used for therapeutic purposes as compared to years before the ban. The antimicrobials now used are classes such as tetracyclines that are also used in humans.[51]
- Resistance to some antibiotics has decreased in some animals while resistance to other antibiotics has increased.

In humans –

- 35.6 % increase in Defined Daily Doses[b] from 1999-2008
- Vancomycin, quinopristin/dalfopristin, avilamycin resistance still prevails more than a decade after banning the use of avoparcin, virginiamycin, and avilamycin for growth promotion.
- Resistance to virginiamycin (quinupristin/dalfopristin, e.g., Synercid) in humans had been steadily increasing (up to 25%) from 1997 to 2005 until the definition of resistance was changed in 2006[52], bringing the level of resistance down to 0%.[c]
  - When the definition of resistance is standardized to the United States definition used by CDC and the level of resistance in humans in Denmark to Synercid is compared to the United States, we find that the level is 10 times higher in Denmark in spite of the Danish ban in 1998 of use in animals and the continued use in the United States.

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[a] Trends in total consumption (kg active compound) of prescribed antimicrobials for production animals reported by DANMAP 2008; Table 5

[b] Defined Daily Dose is a measure of antimicrobial use in human medicine in Denmark

[c] The rationale for this change is unknown, but appears to introduce bias in reporting. DANMAP decided to use a preliminary European Committee on Antimicrobial Susceptibility Testing breakpoint instead of the previously used breakpoint established by the Clinical and Laboratory Standards Institute.

In humans and animals –

- A significant increasing trend of resistance to tetracycline, ampicillin, and sulfonamide in humans and pigs from 2001 – 2006 (2007 and 2008 decreases are related to in an increase in outbreaks of sensitive strains)

- There is little evidence to demonstrate a general decline in antimicrobial resistance in humans and there is no evidence of an improvement in clinical outcomes of antimicrobial treatment of humans, the desired consequence of the antibiotic ban in livestock. The results have been mixed. In fact, resistance in humans to some of the banned drugs has increased dramatically.

This data indicates that the ban of antibiotic growth promoters in Denmark has not achieved a decrease in total use or a decrease in therapeutic use and mixed results in resistance levels in pigs (an increase in some resistance levels for some antibiotics and a decrease in resistance levels for others).

The ban on antibiotic growth promoters in Denmark has not resulted in a significant reduction of antibiotic resistance patterns in humans. It has, however, resulted in an increase in disease and death in the swine herds and an increase in the use of antimicrobials for therapeutic uses in swine herds that discontinued the use of antibiotic growth promoters.

Even though the results of the Danish experiment with antimicrobial growth promotant drug bans is very mixed, evidence shows that the Danish ban has caused animal health and welfare problems, without significantly improving human health.

Based on the results of the bans enacted in Denmark and the Netherlands, we do not believe the public would significantly benefit from such limitations on the use of antimicrobials. The loss of approved uses of antimicrobials will negatively impact animal health and welfare without significantly or predictably improving public health. Non-science based, broad bans of preventive uses of antimicrobials have the potential to harm public health, such as through increased foodborne disease.

Significant decisions regarding animal health need to be science- and risk-based decisions. Decisions made without the benefit of veterinary input as well as a thorough evaluation of risks and benefits have the potential to further divert resources away from more appropriate disease control measures.

NARMS

Important resistance trends [a] reported by NARMS[53] (Isolates from humans with clinical disease) indicate substantial decreases in *Salmonella* resistance for some serotypes associated with animal sources and an increasing trend in resistance for the serotype associated with human reservoirs:

Salmonella spp. (non-Typhi) – more than twice as likely to be resistant in 1996 as compared to 2007

- a highly significant[b] improvement in susceptibility[c] (22.5% relative increase in susceptibility, from 66.2% in 1996 to 81.1% in 2007)

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[a] Odds ratios were calculated based upon available data from NARMS assuming the reported isolates were representative of the bacterial population.

[b] "Marginally significant" indicates a p-value between 0.05 and 0.10; "significant" indicates a p-value between 0.01 and 0.05; "highly significant" indicates a p-value of less than 0.01

[c] no resistance detected to any of 5 subclasses of antibiotics

Salmonella Typhimurium – more than twice as likely to be resistant in 1996 as compared to 2007

- a highly significant improvement in susceptibility (52% relative increase in susceptibility from 37.9% in 1996 to 57.6% in 2007)

Salmonella ser. Typhi (a human reservoir foodborne pathogen) - more than 4 times as likely to be resistant 2007 as compared to 1999

- a highly significant **decline** in susceptibility (50% relative increase in susceptibility from 71.3% in 1999 to 35.4% in 2007)

Most foodborne infections do not require treatment with antimicrobials. The data indicates that there is a decreasing trend of foodborne diseases, thereby decreasing the potential numbers of treatments.[54] NARMS[55] reports the following resistance percentages of non-typhi *Salmonella* to fluoroquinolone (ciprofloxacin) – 0.1%; third-generation cephalosporin (ceftriaxone) – 0.4%; ampicillin – 10.1%; and co-trimoxazole (trimethoprim-sulfamethoxazole) – 1.5%. These resistance levels do not indicate a public health crisis associated with foodborne *Salmonella*. Resistance patterns from Campylobacter and E. coli do not mirror Salmonella on a drug by drug basis, but do show overall increases or stability in susceptibility levels. Of note, campylobacter resistance to ciprofloxacin (a fluoroquinolone) has continued to increase following the ban on enrofloxacin. The trends of decreasing resistance (increasing susceptibility) mean more successful treatments when needed. This information would suggest that there is not a public health crisis related to foodborne pathogens.

Conclusion

The American Veterinary Medical Association is committed to ensuring a safe and healthy abundant food supply. Among other things, our profession is dedicated to improving animal health, further safeguarding public health and food safety, and to maintaining the long-term effectiveness of antibiotics. The AVMA established a profession-wide initiative to create and implement judicious use guidelines for the therapeutic use of antimicrobials by veterinarians, and we launched an educational campaign to raise the awareness of the profession to the issue. Today, we continue to review and update those guidelines to reflect current practices and actively encourage compliance.

Foodborne illness and the spread of antibiotic resistance is a public and animal health concern. There is no question that the public demands a safe food supply and that the human medical profession is facing extreme challenges because of hospital- and community-acquired resistant human pathogens. The human medical problem with resistant nosocomial and community-acquired infections has increased the concern of development of resistant pathogens in animals that can be transferred to humans through the food supply or environment. Yet, we must not forget that animal health is food safety.

The AVMA shares the concerns of the human medical community, the public health community, governmental agencies, and the public regarding resistance developing in animals and then being transferred to humans. However, we emphasize the importance and primacy of using these medicines to prevent and treat diseases before they enter our food supply. Preemptive bans of veterinary antimicrobials before science-based studies and risk-based evaluations are performed can be detrimental to animal and human health. Simple solutions may not solve such complex problems. Inappropriate reactions could have unknown and unintended consequences that negatively affect animal health and welfare, and ultimately, could create other public health risks, such as increased foodborne illness.

The AVMA believes that a lack of availability of antimicrobials or other therapeutic agents in veterinary medicine and animal agriculture can put animal health and welfare and public health at risk. We encourage a regulatory strategy that is based on science, risks and benefits analyses, and cooperation with all relevant stakeholders.

An analysis that compared the regulatory strategy of the European Union to broadly ban or restrict animal antibiotic uses with the United States' approach of continued prudent use to prevent and control animal

infections, together with measures to improve food safety, has some pertinent conclusions. Among these, prudent use of animal antibiotics may actually improve human health, while bans on animal antibiotics, may inadvertently harm human health.[56]
The AVMA supports the ongoing scientific efforts of monitoring and surveillance of foodborne disease and resistant foodborne pathogens; education; development of new antimicrobials, biologics, and other treatment options; and other research to better define the challenges presented by animal agriculture. Increased data collection and surveillance of disease, as well as continued veterinary input (including the appropriate use of pre- and post-harvest interventions, and compliance with judicious use guidelines for veterinarians and producers), may be sufficient to protect human health against the current small risks without compromising the health of food animals.

We also support adequate funding for all efforts to improve animal health and food safety, including efforts to combat antimicrobial resistance. These efforts were high-priority tasks in the 2001 version of the Public Health Action Plan to Combat Antimicrobial Resistance that was created by a Federal Interagency Task Force on Antimicrobial Resistance. Of the original 13 Top Priority Action Items, few actions have targeted animal health or yielded results that can mitigate antimicrobial resistance in animals, and therefore transmission to humans. The Action Plan reflected a broad-based consensus of federal agencies and stakeholders on actions needed to address antimicrobial resistance and provided a blueprint for specific, coordinated federal actions that included the full spectrum of antimicrobial use: human medicine, veterinary medicine and animal agriculture. We are disappointed that the Action Plan was not adequately funded and prioritized by Congress. We are also concerned that recent versions of the Action Plan do not appear to not be as collaborative, broad-based, or acceptable to the diverse community of stakeholders.

The AVMA is committed to working in concert with the CDC, FDA, and USDA to provide consumers – not only in the United States, but all over the world - with the safest food possible. The judicious use of antimicrobials is but one of the essential components of the process that enables animal agriculture to meet that demand. Other components include veterinary care, good management practices, biosecurity, proper nutrition and good husbandry.

Thank you for the opportunity to appear before you today and speak on behalf of our profession.

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Ms. SCHAKOWSKY. Thank you, Dr. Hoang.
Dr. Singer.

STATEMENT OF RANDALL SINGER

Dr. SINGER. Mr. Chairman and members of the subcommittee, I would like to thank you for giving me the opportunity to discuss the role of antibiotics in animal agriculture. My name is Dr. Randall Singer. I am an Associate Professor or epidemiology at the University of Minnesota, both in the College of Veterinary Medicine and in the School of Public Health.

Antibiotic resistance continues to be a critical issue that affects human health, animal health and environmental health. All uses of antibiotics have the potential to select for resistant bacteria. What we are discussing here today, though, is risk and specifically the potential that the use of antibiotics in animal agriculture might result in more antibiotic-resistant bacteria that then lead to increased human health harm.

One of the antibiotic uses that is of particular concern is the approved label claim of growth promotion. The fact is that this label claim is almost 50 years old. It is an unfortunate label whose name has never been changed. Unfortunate why? Because we now know that the reason these antibiotics help animals grow faster is because these antibiotics help animals maintain their health status. They prevent disease as well. And for evidence of this, we need to look no further than the Danish experience. It is a fact that following the removal of growth-promoting antibiotics in Denmark, the animals got sicker. Animal diseases that had been kept under control now appeared as a quote from their papers, epidemics, as stated by the Danish themselves. The unfortunate truth is that more than 15,000 swine producers in Denmark, over 60 percent of the total that existed before the ban, went out of business, most of these being the small and mid-sized farms.

But let us not focus on productivity. When it comes to antibiotics, we should be thinking about impacts on health. The only documented health benefit of the ban in Denmark was a decrease in some resistance in some bacteria on farms and in the community. There was no real human health benefit related to fewer resistant infections, at least that I have seen reported from the Danish experience.

Regardless, perhaps it is time to retire the outdated label claim of growth promotion. After all, its name implies a strictly production use of antibiotic. But let me ask you this. Since when it has become better to treat the sick than to prevent the disease in the first place? If we can give a lower dose of a second-tier antibiotic to animals to prevent a disease from occurring by, for instance, improving the gut health of that animal, isn't this better than having to treat an entire population of sick animals with a high dose of a critically important antibiotic? The growth promotion doses give us that option.

We need to take a holistic view of health that seeks to maintain the healthiest animal population possible. Healthier animals lead directly to a safer food supply. Nobody in the animal industry wants to continue, though, with the status quo. Changes in production are happening. Companies are voluntary reducing their uses

of antibiotics. But we still need options for preventing and treating disease and these are disappearing as can be seen in the poultry industry. The only animal agricultural antibiotic banned from use in the United States remains the fluoroquinolones in poultry production. There is another antibiotic. It has no human counterpart and it still has not been approved for treating disease in poultry in the United States. Both of these antibiotics are available as treatment options in Europe. I will stress that again. Fluoroquinolones are available in Europe as a treatment option.

In the absence of efficacious treatment options, the poultry industry at least needs the option of using antibiotics to prevent disease in the first place. What we should be doing is determining what antibiotic uses minimize risks to human health while maximizing animal health. How do we begin to quantify those risks and determine the antibiotic uses that pose the least risk? FDA's Center for Veterinary Medicine has an approved risk assessment approach as described in Guidance for Industry Document number 152. I was part of a team that used this approach to examine a specific antibiotic class, and we found that under the FDA's own definition, there was reasonable certainty of no harm to human health associated with this use. That is a peer-reviewed publication.

I am in full agreement with the many international reports and FDA statements that we need to continue to assess these risks but they need to be done a drug-by-drug basis in each animal species. All antibiotics that fall under the same usage category are not equal in terms of their impacts on resistance or their impacts on human and animal health.

In conclusion, Mr. Chairman and members of the subcommittee, I thank you for the opportunity to speak today. Antibiotics are an integral component of animal health and healthier animals lead to healthier people. I would hope that decisions regarding antibiotics, their approval and removal from use will continue to rest with the FDA's Center for Veterinary Medicine, who has in place a system for assessing the risks to human health associated with animal antibiotic use. I hope that those who make the final decisions about antibiotic use are truly interested in all health, human, animal and environment, and agree that preventing disease is always preferable to having to treat the sick. The best way to manage antibiotic uses in animal agriculture is through sound, rational, science-based policy that evaluates the risks and benefits of all antibiotic uses. Thank you.

[The prepared statement of Dr. Singer follows:]

Testimony of Dr. Randall Singer

Associate Professor of Epidemiology

University of Minnesota

Subcommittee on Health

Committee on Energy and Commerce

United States House of Representatives

Antibiotic Resistance and the Use of Antibiotics in Animal Agriculture

July 14, 2010

Mr. Chairman and Members of the Subcommittee:

Thank you for providing me with the opportunity to discuss the important topic of antibiotics in animal agriculture. I am an Associate Professor of Infectious Disease Epidemiology and Ecology at the University of Minnesota. I have a dual appointment at the university, both in the College of Veterinary Medicine and the School of Public Health. I am a veterinarian by training with a degree from the University of California at Davis. Following my veterinary degree, I obtained a PhD in epidemiology from the University of California at Davis. I have worked as a professor of epidemiology since 1999, first at the University of Illinois, Urbana-Champaign and now at the University of Minnesota. I have spent the past 12 years engaged in research, teaching and service activities related to antibiotic use and antibiotic resistance in human and animal health. I will focus my discussion on six questions that I think are critically important:

1. What are antibiotics and how are they used in animal agriculture?
2. What is antibiotic resistance and how does it develop?
3. What are the impacts of antibiotic usage in animal agriculture?
4. How do we assess the risks of antibiotic use in animal agriculture?
5. How do we manage the risks of antibiotic use in animal agriculture?
6. How does the *One Health* paradigm apply to antibiotic use in animal agriculture?

What are antibiotics and how are they used in animal agriculture?

Although many people think of antibiotics as human-made compounds, antibiotics are actually small molecules that are naturally produced by microorganisms in the environment (30). Humans have created synthetic analogs to these naturally occurring compounds to improve their efficacy. The function of these molecules in nature is still not entirely understood. Because bacteria in the environment have been exposed to these antibiotics for eons, they have developed mechanisms for survival in the presence of these compounds. These mechanisms are what we refer to as antibiotic resistance -- a way for the bacterium to resist the action of these antibiotics. The presence of naturally produced antibiotics in the environment is rarely considered as a contributor to the degree of resistance that is found in bacteria around the world, and yet it is this environmental pool of resistance, recently termed the resistome (7), that is the basis for the resistance observed today. Antibiotic resistant microorganisms can be found in areas with little to no obvious human influence or impact, emphasizing that there is a large background reservoir of resistance that exists in the natural world.

Antibiotics are used in animal agriculture in four major ways: *disease treatment, disease control, disease prevention*, and *growth promotion*. Briefly, disease treatment refers to the use of the antibiotic in an ill animal. Disease control refers to the use of the antibiotic in a population of animals during a time of illness. Not all of the animals receiving the antibiotic are necessarily ill at the time of antibiotic administration. Disease prevention refers to the use of the antibiotic in an animal or in a population of animals at a time when it is known that the animals are susceptible to disease and a disease risk is present. The importance of prevention should not be underestimated; it is always preferable to prevent disease than to treat a whole flock or herd of diseased and exposed animals once an outbreak has begun. In fact, one of the central tenants of medicine is to minimize health impacts by maintaining a healthy population in the first place. Finally, growth promotion refers to the use of the antibiotic in a low-dose fashion to improve the weight gain and feed efficiency of the animal. This type of use has been termed "production use" in the recent FDA Draft Guidance document #209 because production uses "are not directed at any identified disease, but rather are expressly indicated and used for the purpose of enhancing the production of animal-derived products (e.g. increasing rate of weight gain or improving feed efficiency)" (28).

All four of these use categories result in an improved health of the animal receiving the antibiotic. Nonetheless, assumptions about these uses often lead to confusion. One area of confusion is related to the route of administration. Uses of antibiotics that are "in-feed" are often equated with growth promotion uses and are assumed to be long-term low-dose regimens of antibiotic administration for the sole purpose of improving weight gain. In fact, all four of these

uses can be applied via the feed or the water because the only realistic way to administer an antibiotic to populations of animals, such as a flock of chickens, is through the feed or the water. Further, antibiotics used for disease treatment and disease control are often given via the drinking water because sick animals may stop eating but often continue to consume water.

Many of the antibiotics currently used in animal agriculture, particularly those used for "production" purposes, were approved in the 1960's. In general, there was a poor understanding of how these compounds worked, but because animals fed antibiotics for production purposes grew faster, the antibiotics were labeled for increased feed efficiency and average daily weight gain. The label claims for these antibiotics have not changed in almost 50 years. In a time when bacteria are becoming increasingly resistant to the action of antibiotics, it might seem injudicious to use an antibiotic solely to increase weight gain and feed efficiency, and this use might be interpreted as having a pure economic value. We now know that low-dose uses of antibiotics improve the overall health of the growing animal, and the outdated label claims of feed efficiency and growth promotion do not do justice to the "gut health" and "disease prevention" attributes that these low doses possess. In general, the improvements seen in feed efficiency and growth are the result of improved health and gut integrity due to disease prevention.

When strictly considering the label claims of improved feed efficiency and average daily weight gain, the "production" uses of antibiotics do not appear to have the same importance they once had. For example, in a study by Dritz *et al.* (9), various antibiotic regimens were tested on growing pigs. Only the growth rate of nursery pigs was significantly improved by some of the regimens. The authors concluded that dramatic improvements in the health management of animals in intensive agricultural facilities as well as improved animal genetics likely led to a diminished need for "production" uses of antibiotics.

A very recent study by Aarestrup *et al.* (2) analyzed antibiotic use and production data from swine raised in Denmark between 1992 and 2008. By January 2000, Denmark had stopped using any antibiotic for growth promotion in swine. The authors concluded that total antibiotic consumption per pound of pig produced decreased over the time span of the study, although the authors included approximately 6 years of data before the ban was even initiated. At the same time, the authors concluded that swine productivity, when analyzed as mean number of pigs per sow per year raised for slaughter and average daily weight gain increased during the time period of the study. Consequently, it would appear from this study that animals can be raised efficiently without the need for "production" uses of antibiotics.

There are several troubling aspects of the data analysis in the paper by Aarestrup *et al.*, however, as well as a key take-home message that was not highlighted in the manuscript. First, according

to the Danish Agriculture and Food Council, the number of pig producers in Denmark dropped from approximately 25,000 in 1995 to less than 10,000 in 2005. Only those with the highest productivity and efficiency survived, and those producers that survived became larger operations and became more integrated and intensive. If more than half of the producers were lost during the timeframe of the study, and if these producers were the least efficient and productive, then estimates of overall productivity would have to increase over time *for no other reason than the fact that only the most productive producers survived.* Unfortunately, information about specific producers and their productivity over time is not available, and therefore it is impossible to do an analysis to determine how much increase there was in productivity on an individual producer basis. Even with this information, though, the fact remains that increases in pig productivity were already being observed in Denmark prior to the bans due to improved animal genetics and improved health management systems.

A final point that is critical to recognize from the paper by Aarestrup *et al.* is demonstrated in Figure 2 of the paper, as shown below:

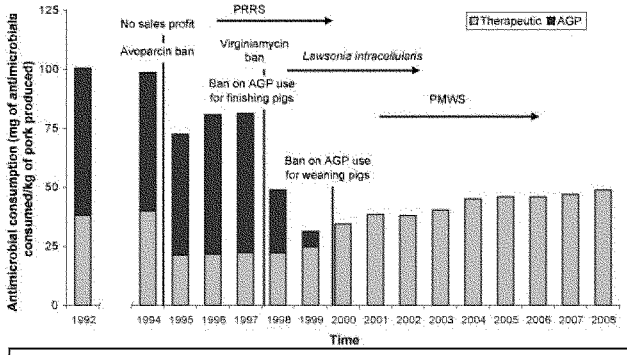


Figure 2 (from Aarestrup et al., 2010 (2) — Consnmption of antimicrobials for use as AGPs (black bars) or for therapeutic administration (gray bars) from 1992 to 2007 by the Danish swine production system. Notice the ban on use of avoparcin and on veterinary profits from the prescription and sale of antimicrobials, the ban on AGP use in finishing pigs and on nse of virginiamycin in all pigs that was instituted in 1998, and the ban on AGP use in weaning pigs that was instituted in January 2000. Outbreaks of PRRS (1996 to 2000), disease attributable to *Lawsonia intracellularis* (1998 to 2002), and PMWS (2001 to 2006) are indicated (arrows). Weaning and finishing pigs weighed < 35 kg and > 35 kg, respectively.

Over time, and particularly following the ban on growth promoting antibiotics (AGP), there was a steady increase in the use of therapeutic antibiotics. The antibiotics approved for therapy in animal agriculture are often those that would also be considered medically-important in humans.

The authors attempted to explain these increases in therapeutic antibiotic uses by events like an outbreak of *Lawsonia intercellularis* in the period of 1998 through 2002. This is misleading because *Lawsonia intercellularis* is always present on most swine operations and can be kept in check by the administration of disease prevention doses of antibiotics. A take-home message of this paper is the fact that this disease appeared following the removal of "production" uses of antibiotics and should indicate that these uses do have health-related functions far beyond the labeled feed efficiency and average daily weight gain claims. Such uses might include disease prevention doses of antibiotics that would be targeted at specific pathogens typically found on farms, such as *Lawsonia intracellularis*, and would be given to swine at ages when they are most susceptible (i.e. at weaning).

What is antibiotic resistance and how does it develop?

Antibiotic resistance refers to the ability of a microorganism to survive the effects of an antibiotic. As stated previously, antibiotics are naturally produced by environmental microorganisms, and as a result, many microorganisms possess mechanisms that enable them to resist the action of these antibiotics. The two major mechanisms by which the microorganism can acquire resistance are through random changes in the genetic makeup, known as mutation, or through the sharing of genetic material with other microorganisms.

When an antibiotic is applied to a population of bacteria, those bacteria that are not intrinsically resistant to its action must find a way to survive. The antibiotic will either kill or suppress the bacteria that are susceptible to the antibiotic. For this reason, the antibiotic is said to 'select' for resistant bacteria because only the resistant ones can survive despite the pressure imposed by the antibiotic. During the course of the antibiotic, the rates at which bacteria can acquire resistance might increase. Consequently, the use of the antibiotic may pose a risk to human and animal health through the selection of a more resistant bacterial population.

Whereas FDA Guidance Document #209 (28) states in the Executive Summary that "Misuse and overuse of antimicrobial drugs creates selective evolutionary pressure that enables antimicrobial resistant bacteria to increase in numbers more rapidly than antimicrobial susceptible bacteria and thus increases the opportunity for individuals to become infected by resistant bacteria," it is important to recognize that ALL uses of antibiotics select for resistance to some degree in specific bacteria. The question, stated simply, is how to ensure that public health and environmental health are maximized while maintaining animal health. To address this type of holistic question, we must first assess how different uses of antibiotics impact antibiotic resistance.

What are the impacts of antibiotic usage in animal agriculture?

To begin this section on the potential impacts of antibiotic use, it is critical to distinguish between antibiotic resistance and food safety. Nobody should be questioning the fact that bacteria from animals can move through the food chain and cause disease in people. This is the basis of food safety and control programs designed to reduce the burden of illness associated with foodborne disease. Efforts are often focused on controlling the contamination of food products and educating the consumer about the proper ways for handling food products. Foodborne bacteria can cause disease regardless of whether they are susceptible or resistant to antibiotics. The relevant question for this hearing is why are some of these bacteria resistant to antibiotics in the first place, and did the use of antibiotics in animals cause the resistance observed in these bacteria? Unfortunately, many individuals have linked the two issues, leading to the assumption that antibiotic resistant bacteria that infect people through the consumption of food are resistant BECAUSE of the use of antibiotics in animals. This linking of two separate issues has been incorporated into many reports that are being used to set policy, and because many of these reports cite prior reports rather than citing the original research on which the reports are based, these misconceptions have been propagated over time. Two key examples are described below:

One study that was published in 1999 out of Denmark reported on a multi-drug resistant bacterial isolate of *Salmonella* Typhimurium definitive phage type 104 that caused morbidity and mortality in people (20). This bacterium was of particular concern not only because it was multi-drug resistant but also because it was resistant to a very important class of antibiotic, the fluoroquinolones. The authors of this paper concluded in the Abstract that "because of this increase in quinolone resistance in *Salmonella*, the use of fluoroquinolones in food animals should be restricted." If one reads beyond the Abstract of this paper, the authors admit that "There was no indication of fluroquinolone use in the implicated [swine] herds" (p. 1424). They continue to say that it is impossible to determine if this multi-drug resistant *Salmonella* strain "was introduced by pigs from outside Denmark, was introduced by environmental spread (e.g., from wild animals or equipment), or was related to the use of fluoroquinolones at the suspected farms before 1998" (p. 1424). Consequently, this paper is an unfortunate story of severe illness caused by *Salmonella* that potentially originated in swine, but it says nothing about the impacts of the agricultural use of antibiotics. It should be noted that fluoroquinolones, when used in animal agriculture, are used as a therapeutic antibiotic for treating sick animals; they are not "production use" antibiotics. To include this paper in discussions of the potential risks of agricultural uses of antibiotics and in discussions regarding "production use" antibiotics, as has been done in many of the governmental and non-governmental reports on antibiotics in agriculture, seems inappropriate.

A second paper worth noting was published in 2000 and discussed a ceftiofur resistant *Salmonella* strain that was acquired by a child possibly from cattle (11). Ceftiofur is a third-generation cephalosporin related to ceftriaxone, a medically-important antibiotic. In the Abstract, the authors conclude that "This study provides additional evidence that antibiotic-resistant strains of salmonella in the United States evolve primarily in livestock." A statement this strong would suggest that the authors had data demonstrating that ceftiofur was used in the implicated cattle herd, that susceptible *Salmonella* strains were isolated, and that they could document the emergence of a ceftiofur-resistant strain on the implicated farm due to the use of the antibiotic on that farm. The authors state on page 1247 that "It is probable that the use of antimicrobial agents in cattle led to the selection of the ceftriaxone-resistant strain that was subsequently transmitted to the child. Although we were unable to establish its use in these herds, an expanded-spectrum cephalosporin (ceftiofur) is approved for use and is widely used in domestic animals, including cattle." This paper documents an unfortunate severe illness but says nothing about the impacts of antibiotic use in animal agriculture. Once again, the antibiotic addressed in this study, ceftiofur, is a therapeutic antibiotic and should not be included in discussions of "production use" antibiotics. Nonetheless, it remains one of the central citations used to set policy

Studies that have been conducted on the effects of antibiotic administrations in agricultural animals are not numerous. There are more studies on the effects of treatment dose administrations than on the effects of disease prevention and "production" dose administrations. More studies need to be performed in animals in various settings meeting rigorous study design requirements. Dosing regimens need to be evaluated to determine how they impact selection of resistant bacteria. A brief summary of several studies that have evaluated antibiotic administrations are described below.

A series of studies has been conducted in dairy and beef cattle to explore the effects of therapeutic ceftiofur administration on the appearance of ceftiofur-resistant *E. coli*. In one study, treated dairy cows showed a significant decrease in the total *E. coli* population when fecal samples were analyzed (24). There appeared to be a complete decimation of the susceptible *E. coli* population. Animals that possessed *E. coli* with ceftiofur resistance could be detected in some of these samples. Although animals not treated with ceftiofur were confirmed to possess ceftiofur resistant *E. coli* using molecular methods, these animals never had resistant *E. coli* isolated from their fecal samples. Within a week of the cessation of treatment, the susceptible population of *E. coli* returned, and resistant isolates were not recovered again for the remainder of the 30-day study period. The antibiotic treatment provided a window to detect the presence of ceftiofur-resistant *E. coli* but did not cause its emergence or result in its amplification. In a trial with ceftiofur in beef cattle, similar findings were observed (17). In this study, the susceptible *E.*

coli population returned within 28-days, indicating that the effect in this study was somewhat longer lasting. Another study in dairy cattle found that treated animals continued to shed resistant strains 17 days after the initial treatment (16). In an investigation of dairy farms, those dairies that used ceftiofur were significantly more likely to have cows shedding *E. coli* with reduced susceptibility to cephalosporins (26).

These studies and others not mentioned demonstrate a consistent point: high dose therapeutic antibiotic administration can eliminate susceptible populations of bacteria. This effect can lead to a selection of resistant strains. Furthermore, many of the antibiotics used for therapeutic purposes in animals would be considered medically-important to humans, and consequently, their use could be selecting for bacteria that are resistant to the same antibiotics used in human medicine. Further research is needed to determine how to minimize this risk and also how to control the release of resistant bacteria from the farm.

Studies on antibiotic uses at "production" and disease prevention doses can also show a higher rate of resistance in the treated animals versus the control animals. For example, in pigs treated with apramycin (an antibiotic no longer marketed in the US), apramycin resistant *E. coli* levels were higher in the treated versus the control groups but quickly returned to baseline levels as in the previously cited treatment dose studies (18,19). Effects such as these are not always observed, as evidenced by a recent study of feeding trials in finishing pigs with tylosin or chlortetracycline under different dosing regimes (29). This study found no difference in resistance in either *Salmonella* or *E. coli* between the treatment and control groups. Another effect occasionally assessed in these studies is the potential for the low-dose antibiotics to decrease shedding of important foodborne bacteria such as *Salmonella*. This effect has been suggested by studies that have observed lower levels of *Salmonella* shedding in pigs that have been fed antibiotics (10,12,19). One recent study observed a decrease in *Salmonella* shedding over time in the antibiotic-treated groups, but the effect was not statistically significant (29).

Perhaps the best place to look for some of the impacts that "production" uses of agricultural antibiotics have is in Denmark and the European Union. It is often reported that levels of antibiotic resistance in bacteria isolated from animals and people in Denmark declined following the complete ban of "production uses" of antibiotics in the late 1990's. Furthermore, it is often stated that antibiotic use levels also declined. Both of these statements, however, depend on how the data are analyzed.

Figure 27 from the 2008 DANMAP report (8), shown below, shows that the prevalence of resistance to certain antibiotics in *Salmonella* Typhimurium has actually increased over time.

This is important because of the public health relevance and burden of illness associated with this bacterium.

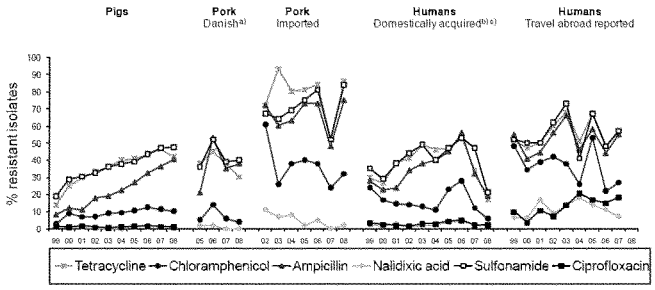


Figure 27. Trends in resistance to selected antimicrobials among Salmonella *Typhimurium isolated from pigs, pork and from human cases, Denmark*

Figure 28 from the 2008 DANMAP report (8), shown below, demonstrates increasing prevalences in antibiotic resistant *Campylobacter jejuni*, another important human pathogen.

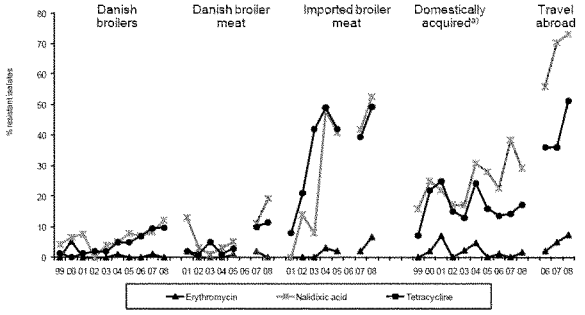


Figure 28, Trend C. jejuni. Trends in resistance to selected animicorbials among Campylobacter jejuni *isolates from broilers, broiler meat and human cases, Denmark*

Together, these figures demonstrate that the removal of antibiotics from animal production will not necessarily result in a decline in antibiotic resistance. Figures 9 and 10 from the 2008 DANMAP report (8), shown below, highlight a critical concern when setting antibiotic use policy. When the antibiotic administrations are recorded as the number of doses given to animals, the number of doses has steadily risen in Denmark since the ban of "production use" antibiotics. These Figures, when combined with Figure 2 from Aarestrup et al. as shown previously (2), clearly demonstrate that following the removal of the "production use"

antibiotics, considerably more therapeutic administrations were required. This is due to the increased animal illness that has been observed in Denmark since the ban.

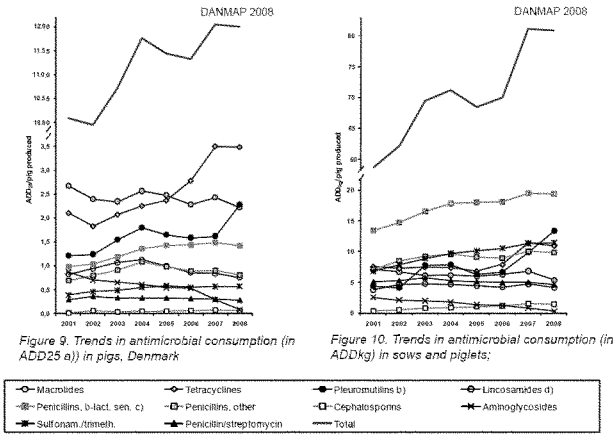


Figure 9. Trends in antimicrobial consumption (in ADD25 a)) in pigs, Denmark

Figure 10. Trends in antimicrobial consumption (in ADDkg) in sows and piglets;

Given that over ten years ago the removal of the "production use" antibiotics in Denmark was implemented to improve human health, one would expect to have seen human health improvements by this point in time. The major impacts that are cited are a reduction in resistant bacteria in animals and in people within the community; no clear-cut human health improvements (i.e. decreased incidence of disease caused by resistant bacteria) are even mentioned. As shown previously, even the reports of decreased antibiotic resistance in bacteria from animals and humans depends on which bacteria and which antibiotics are being considered.

On the contrary, the 2008 DANMAP report (8) documents the dramatic increase in multidrug-resistant *Klebsiella pneumoniae* isolates in hospitals. This bacterium can cause serious blood infections in people, and the multidrug-resistant strains are particularly difficult to treat. One hypothesis for the dramatic increase is the increased consumption of broad spectrum antibiotics, especially tbe 2nd and 3rd generation cephalosporins. Much of this consumption is occurring in human hospitals, but some of this consumption could also be occurring as a consequence of the increased use of therapeutic antibiotics on farms to treat the increasing numbers of ill animals.

How do we assess the risks of antibiotic use?

There are two primary approaches for assessing and managing the potential risks associated with antibiotic use in animal agriculture. One approach is to employ the precautionary principle. In this argument, the precise public health risks associated with animal antibiotic use might not be known. Because there is a perceived potential for serious negative consequences, it is deemed better to avoid the action entirely rather than to suffer the potential consequences. Europe has used this principle to withdraw certain antibiotic uses from animal agriculture (3). One reason why this approach is often relied upon, especially in the case of antibiotic use and resistance, is the belief that antibiotic use is negatively impacting human health. It is extremely difficult to design, implement and analyze the decisive study that will prove or disprove this theory. Caution would dictate that by the time such a study is complete, any negative effects associated with continued antibiotic use might be irreversible. Therefore, the precautionary principle approach to managing antibiotic use in animal agriculture has only one real option: withdraw the antibiotic use that might result in a negative human health consequence. The problem is that it is very difficult if not impossible to predict the negative unintended consequences associated with a precautionary measure (6).

A more objective way to evaluate the potential consequences of antibiotic use in livestock and poultry is to develop scientifically-based predictions, and through these models, evaluate interventions that reduce potential human and animal health risks associated with certain antibiotic uses in animal agriculture. This approach includes the methodology known as risk assessment. Throughout many governmental and non-governmental reports, including those cited in FDA Draft Guidance #209 (28), there have been repeated calls for the use of risk assessment approaches. In 2003 the FDA Center for Veterinary Medicine (FDA-CVM), which uses a scientific approach to regulatory decisions, issued Guidance for Industry document #152 that described a qualitative risk assessment process that is utilized in the approval of all applications for new animal antibiotics and the reassessment of existing animal antibiotics (27). FDA Guidance Document #209 makes a clear distinction between the use of #152 in the pre-approval process of a new animal drug and a safety review of a currently-approved product. Regardless, the risk assessment approach is a science-based approach to evaluating the potential risks to human health associated with the use of antibiotics in animal agriculture. A major challenge to this approach, though, is related to the definition of risk and an acceptable level of risk. In FDA Guidance Document #209, it is stated on page 13 that "FDA considers an antimicrobial new animal drug to be "safe" if the agency concludes that there is "reasonable certainty of no harm to human health" from the proposed use of the drug in food-producing animals" (28). This is a vague definition that has traditionally been used for toxicological

assessments. With respect to antibiotic resistance, it is unclear what is implied by "reasonable certainty of no harm."

If the risk assessment approach is to be utilized, it should be expected that each antibiotic or class of antibiotic that is approved or that is seeking approval would be evaluated separately, and that an assessment would be conducted in each animal species separately. To assume that all antibiotics that are used in the same way pose the same risk to human health seems to defeat the purpose of a scientifically-sound risk assessment process. Performing a risk assessment that is drug-host-microbe specific is feasible, and there is at least one peer-reviewed and published risk assessment that did this while following the GFI #152 approach. The published model assessed the risk that the agricultural use of a family of antibiotics known as macrolide antibiotics poses to human health (14). The concern is that macrolide antibiotics are also used in human medicine, and therefore, the use of macrolide antibiotics in animal agriculture could compromise the efficacy of these antibiotics in human medicine and potentially increase the number of macrolide-resistant bacterial infections in people. A semi-quantitative risk assessment model following the format of GFI #152 was developed and found that all macrolide antibiotic uses in animal agriculture in the U.S. pose a very low risk to human health. The Table below shows the results of the model. The risk is expressed as the probability that macrolide use in the animal species will result in macrolide resistance in a specific bacterium, that this bacterium will make it through the food chain and infect a person, that this person will seek medical care, and that treatment of the infection with macrolides will fail due to the macrolide resistance. The highest risk was associated with macrolide-resistant *Campylobacter* infections acquired from poultry, but this risk was still estimated to be less than 1 in 10 million and would thus meet the standard of "reasonable certainty of no harm" employed by FDA-CVM.

Animal Product	Macrolide-Resistant Bacteria	Quantified Risk to Humans of Treatment Failure Due to a Resistant Infection
Beef	*Campylobacter*	< 1 in 236 million per person per yr
	E. faecium	< 1 in 29 billion per person per yr
Poultry	*Campylobacter*	< 1 in 14 million per person per yr
	E. faecium	< 1 in 3 billion per person per yr
Pork	*Campylobacter*	< I in 53 million per person per yr
	E. faecium	< 1 in 21 billion per person per yr

Results from Hurd et al., 2004, J Food Prot, 67:980-992

How can we manage the risks of antibiotic use in animal agriculture?

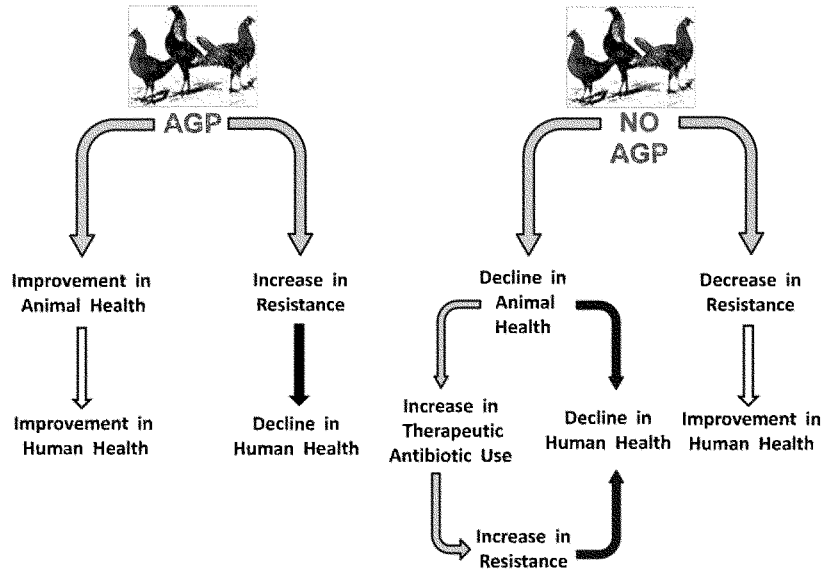
Most risk assessment models conducted to date in antibiotic resistance that have been used for regulatory purposes have not included specific interventions that can be implemented to reduce the human and animal health risks. Instead, the assessments seem to have been designed for the sole purpose of making the dichotomous decision of whether or not to withdraw an antibiotic from use. For risk assessments to be useful, they should include evaluations of potential interventions for reducing the risks to human and animal health. In the U.S. FDA-CVM risk assessment of fluoroquinolone use in chickens (4), the model only estimated the potential human health impact of this antibiotic use and did not evaluate ways for minimizing the risk associated with fluoroquinolone use in poultry. For example, the model could have examined the possibility of processing chickens from treated poultry flocks separately from chickens from untreated flocks as a potential risk reduction strategy. This separated processing could help reduce the chance of cross-contamination of chicken meat from non-treated poultry flocks with the bacteria from treated flocks. The model could have examined a potential intervention in which farms that have received fluoroquinolones are cleaned in a more intensive manner than the normal cleaning, and all litter from these flocks is sterilized. Finally, the model could have assessed an intervention in which flocks that have been treated with antibiotics would have to wait for a longer period of time before processing. This type of approach would resemble the mandatory withdrawal times associated with antibiotic residues. Guidelines could then be developed to determine when specific antibiotic uses should be ceased in flocks before they go to processing in order to reduce the amount of antibiotic resistant bacteria in the birds. Consideration of such risk mitigation interventions rather than complete withdrawal of these drugs would have been very important to poultry veterinarians.

These types of interventions might sound labor-intensive and costly. They are, and that is the point. Under certain circumstances, it might be cost-effective and ethical for a veterinarian to use a powerful antibiotic to control a severe disease in the herd or flock, but this use would then have major repercussions on how the herd or flock as well as the farm are subsequently managed. Producers might not opt for this intensive measure, but at least they would have a choice that is accepted as scientifically-sound for reducing both the human and animal health risks associated with the antibiotic use on their farm. As we begin to gain a better understanding of the ecology of resistance and its relation to animal and human health, we will need these scientifically-based strategies for minimizing the impacts of antibiotic use on animal, human and environmental health.

How does the *One Health* paradigm apply to antibiotic use in animal agriculture?

The health of humans, animals and the environment are intricately related. Many of the challenges we face today, including emerging infectious diseases, antibiotic resistance, food safety and security, and sustainable living exemplify this holistic view of health. The notion of *One Health* incorporates this holistic view and aims to bring a multidisciplinary approach to addressing these complex health issues. The issue of antibiotic resistance serves as an exemplary model for a *One Health* approach. We cannot possibly grasp how microbes are impacted by exposure to antibiotics without an understanding of the dynamics of microbes in the environment, animals, and people (25). Further, we cannot understand the implications of human exposure to bacteria carrying resistance genes without understanding how exposure occurs, how resistance develops, and what the risks of such exposure are.

When we consider the complex issue of antibiotic resistance, we must begin to take a more holistic view of health into consideration. Every action and every policy decision we make that is intended to slow or stop the development and spread of resistance has the potential to have serious unintended consequences. As an example, the removal of growth promoting antibiotics from use in food animals in Denmark resulted in an increased reliance on therapeutic doses of medically-important antibiotics to treat the ill animals. The Figure below shows a schematic of this relationship in which animals that are given antibiotics for growth or disease prevention are healthier, leading to a longer term improvement in animal health. This improvement leads to a safer food supply and therefore improved human health. However, these antibiotics can also select for resistance, which can lead to a decline in human health. If antibiotics used for growth or disease prevention are removed, there will be a decrease in antibiotic resistance, which could lead to improved human health. There will also be a decline in animal health, as seen in Denmark and other countries, which will then lead to an increased use of therapeutic antibiotics to treat the sick animals. This leads to increased antibiotic resistance and a decline in human health. Furthermore, a decline in animal health can lead to a decline in human health through more contaminated meat entering the food supply.



In this schematic, the solid black arrows denote negative impacts on human health while solid white arrows denote positive impacts on human health. AGP represents antibiotics used as for growth promotion, but because the effect of these antibiotics is also to improve animal health, AGP could be substituted with Disease Prevention doses.

The scenario described above has a basis in the published scientific literature. The health status of animals that are processed for meat can potentially affect food safety in two major ways. First, animals that are less healthy may shed higher levels of harmful bacteria, such as *Salmonella* and *Campylobacter*. Second, groups of animals that have experienced illness, either clinically or subclinically, can be smaller in size and more variable in size. Their gastrointestinal tracts can have weaker walls. During processing, these factors can contribute to an increased likelihood of the gastrointestinal tract being ruptured, and this processing error can lead to increased contamination and cross-contamination of the meat and thus increase the risk of human foodborne illness. Reducing animal illness likely plays a critical role in reducing the chances of contamination during processing (13,22). A recent mathematical model was developed to address this relationship shown in the figure above (23). The model demonstrated a large increase in human illness associated with small increases in animal illness, suggesting that agricultural management strategies may have significant impacts on human health. The model

showed that the potential benefits to human health associated with the use of antibiotics in animal agriculture can far outweigh the potential risks. This finding has now been validated by additional studies (5,13,15).

Another example of a potential unintended consequence of antibiotic use policy relates to methicillin-resistant *Staphylococcus aureus* (MRSA). An observation was made that tetracycline resistance was among the resistance carried by MRSA isolates from animals. The concern was that any continued use of tetracycline was selecting for MRSA. A recent study from Denmark found that both MRSA and MSSA (susceptible strains) were resistant to tetracycline, but only the MRSA strains were resistant to zinc (1). Zinc chloride has been used in Denmark as a non-antibiotic alternative following the antibiotic bans, and now it appears that zinc compounds may have selected for the emergence and dissemination of MRSA strains in Denmark.

Summary

In summary, Mr. Chairman and Members of the Subcommittee, thank you again for the opportunity to discuss the role of antibiotics in animal agriculture. Antibiotics are an integral component of animal health. All uses of antibiotics improve animal health, and these improvements in animal health can substantially improve human health. Even "production " uses of antibiotics, which have the unfortunate, decades-old label claim of improving feed efficiency and average daily weight gain, have the clear and documented effect of improving animal health. All uses of antibiotics may also pose a risk, mainly associated with increases in antibiotic resistance. The key is to assess the ability of interventions to maximize the benefits and minimize the risks associated with the agricultural use of antibiotics. Simply removing antibiotics from use in animal agriculture may help reduce some of the antibiotic resistance circulating today, but it might also have severe unintended consequences. The best way to manage antibiotic uses in animal agriculture is through sound, rational, science-based policy. A successful management strategy is one that will optimize human, animal and environmental health. Success should not be measured by implementation of the policy itself (21) but rather through documented health improvements.

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Ms. SCHAKOWSKY. Thank you.
Dr. Carnevale.

STATEMENT OF RICHARD CARNEVALE

Dr. CARNEVALE. Chairman Pallone, Ms. Schakowsky and Ranking Member Shimkus and members of the subcommittee, thank you for the opportunity to appear before you today. I appeared before this committee some time back during the Animal Drug User Fee hearings, and I want to thank the committee for moving that piece of legislation through. We greatly appreciate it.

My name is Dr. Richard Carnevale. I am a veterinarian and Vice President at the Animal Health Institute. AHI is an industry trade association representing companies that make medicines for animals. Before AHI, I spent nearly 20 years at the FDA and USDA working on animal drugs and food supply.

While I submitted more thorough comments for the record, I would like to talk to you today about one simple truth: animals need medicines including antimicrobials. Without safe and effective medications to treat, control and prevent diseases, animal welfare would suffer and deaths would increase. Additionally, as Dr. Singer pointed out, healthy farm animals are critical to safe food. Animal health companies invest in the development of new medicines to provide veterinarians and producers the tools to keep food animals healthy and must be able to rely on a predictable science-based regulatory process.

There has been much debate, as we all know, over the contribution of animal antimicrobial use to resistant bacterial infections in humans. Antimicrobial resistance is a serious public health threat but resistance is not a single problem. It is a problem comprised of several different bacteria/drug combinations that must be examined individually to ascertain risks. For example, some of the most widely recognized resistance problems in humans are in respiratory tract infections and venereal diseases like gonorrhea. In neither of these cases is there any evidence that antimicrobial use in animals is associated with these problems.

Both antimicrobial-resistant and susceptible bacteria can contaminate foods, our food safety system is comprised of multiple layers of protection to reduce their presence. The first layer of protection is a stringent regulatory review process at FDA. Animal antimicrobials must meet all the same requirements as antimicrobials used in humans with two additional requirements. First, sponsors must show that drug residues left in foods are safe for human consumption. Second, the FDA Guidance for Industry 152, which Dr. Sharfstein spoke of, outlines a qualitative risk assessment process for new antimicrobials. This process is designed to estimate and manage the risk of antimicrobial-resistant bacteria that could be transferred from animals to humans.

Quantitative risk assessments have also been conducted and published on key antimicrobials, particularly those used in animal feed. A quantitative assessment is a more detailed review of each step along the food production continuum from farm to table that could contribute to or reduce the presence of foodborne bacteria. These studies have routinely reported extremely low levels of risk.

As Dr. Sharfstein discussed, FDA has announced two new initiatives relative to antibiotics used in food animals. These actions illustrate that the agency has broad authority to take actions it deems necessary to protect public health. AHI welcomes these initiatives and understands the reasons for their concerns. We will, of course, comment in detail to both publications.

A second layer of protection and one of the most important, in my opinion, is reducing bacterial contamination in slaughter and processing plants. Improved hygienic and pathogen-reduction measure in meat and poultry plants under the USDA HACCP pathogenic reduction regulation has significantly reduced bacterial contamination and therefore antimicrobial-resistant bacteria as well.

A third layer is in the multi-agency National Residue Program and National Antimicrobial Resistance Monitoring System to assure antimicrobials are being used properly and according to labels. Judicious-use guidelines which the AVMA representative has spoken about help to ensure that antimicrobials are being used responsibly in food and companion animals.

Finally, USDA has mandated safe food handling labels, and there are extensive food safety education programs that instruct consumers how to properly handle and cook foods to avoid foodborne illness.

Before I close, I want to note that Congress in the last 2 years passed legislation dealing with the use of antimicrobials in animals. The 2008 Farm Bill included a mandate for additional research on antibiotic resistance in food animals and the 2008 Animal Drug User Fee Amendments required FDA to collect antibiotic use data from sponsors by March of 2010. We expect the report from the agency later this year.

Mr. Chairman and members of the subcommittee, there are clear benefits to using antimicrobials to keep animals healthy including attending to animal welfare and assuring food safety. FDA has a stringent review process to ensure that antimicrobials are safe and effective. Monitoring data from the NARMS program as well as public and private risk assessments have shown the process is working. With that said, FDA has recently articulated concerns with the way certain antibiotics are currently labeled and used. The animal health industry is committed to working collaboratively with the agency to address those issues while assuring that important animal health products continue to be available to prevent, control and treat animal disease.

Thank you for the opportunity to appear today and I welcome any questions.

[The prepared statement of Dr. Carnevale follows:]

Testimony of Dr. Richard Carnevale
Vice President, Scientific, Regulatory and International Affairs
Animal Health Institute

Committee on Energy & Commerce
Subcommittee Health

Antibiotic Resistance and the Use of Antibiotics in Animal Agriculture

July 14, 2010

Chairman Pallone, Ranking Member Shimkus, and members of the Subcommittee:

Thank you for holding this hearing on antibiotic resistance and the use of antibiotics in animal agriculture. I am Dr. Richard Carnevale. I am a veterinarian by training with a degree from the University of Pennsylvania, and I am here today on behalf of the Animal Health Institute, a trade association that represents companies that make medicines for animals. Prior to joining AHI about 15 years ago, I served as Deputy Director for the Office of New Animal Drug Evaluation at FDA's Center for Veterinary Medicine and later as Assistant Deputy Administrator for the Office of Science at USDA's Food Safety & Inspection Service. AHI companies work to provide products to livestock and poultry producers that help keep their animals healthy. By doing this, companies contribute to public health and food safety. Research shows that the first link in the chain of producing safe meat, milk and eggs is keeping animals free from disease. AHI companies also develop products that are used for the health and welfare of our companion animals, but today my remarks are focused on the objective of this hearing and animal agriculture.

Food safety starts on the farm, and our companies spend millions of research and development dollars to find new and innovative products to keep farm animals healthy. Some animal health products are used to treat and prevent or control disease in animals while others are used for nutritional efficiency. More recently, products are being developed that will contribute to food safety by reducing bacteria that do not make animals sick but have the potential to make people sick.

Animal health products are subject to stringent, science-based review processes at three federal agencies: pharmaceutical and feed additive products are reviewed by the Food and Drug Administration (FDA) under the Federal Food, Drug and Cosmetic Act, biologic products, or vaccines, are regulated by United States Department of Agriculture (USDA) under the Virus, Serum, Toxins and Analogous Products Act, and animal pesticides are regulated by the Environmental Protection Agency (EPA) under the Federal, Insecticide, Fungicide, and Rodenticide Act (FIFRA). All products are reviewed for safety and efficacy: efficacy, which protects producers by ensuring the products deliver the benefits they promise; and safety, to ensure the products are safe for the animal being administered the drug or vaccine and to ensure the meat from the animal is safe for human consumption and safe for the environment.

One class of products important to the health of food animals is antibiotics. Antibiotics are used by livestock producers, poultry producers, and the veterinarians who work with them to prevent, control and treat often fatal bacterial infections. There are many benefits to animals, producers and consumers that come from the use of antibiotics in animal agriculture:

- Healthy animals reduce the need for greater, more involved disease interventions, and limit the spread of disease and illness that can impact the people that care for animals.
- Animal welfare is improved as a result of veterinarians and producers having the tools to be able to maintain the animal's health.
- Producers are more efficient because they can produce more food from fewer animals. Without antibiotics to treat, prevent, and control diseases, more animals get sick and die with producers losing not only the animal but all the input costs, including feed, that have gone into the animal.
- There are ecologic benefits. Young animals that have their diseases controlled through the use of antibiotics grow faster and more efficiently, thereby using less land and feed to maintain the same herd and flock sizes. Moreover, some studies have shown that certain antimicrobials used in cattle feeds reduce levels of methane emissions.
- Benefits to global food markets. With the concern over food costs and availability in today's economic climate, antimicrobials and other animal drugs that improve animal health and productivity are critical to American agriculture's ability to feed the world's growing population. The Food and Agriculture Organization (FAO) of the United Nations estimates that more than 1 billion people worldwide do not have enough to eat. They propose that one solution is to help producers to raise their output.
- Consumers benefit because healthy animals are needed to produce safe food. Over the past five years, published, peer-reviewed studies have indicated that carcasses from chickens without subclinical diseases are more likely to be free of human foodborne pathogens.[1,2,3,4] Research shows this is due in part to more standardized carcass size, reducing the potential for intestinal breakage during mechanical evisceration.

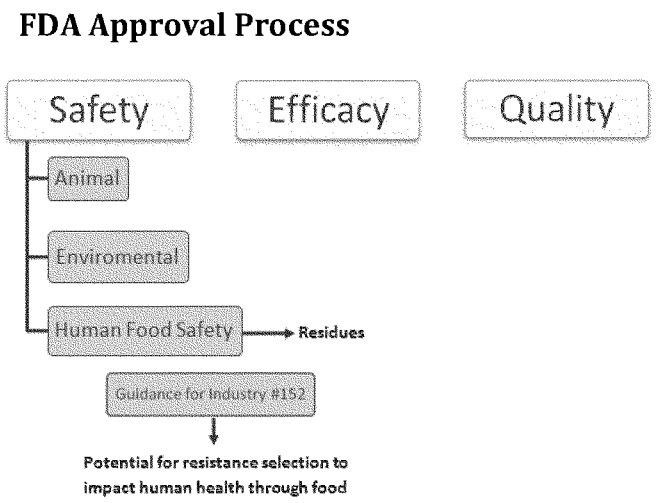
The FDA approves antibiotics to treat specific diseases or conditions at specific dosages rates. There are four specific efficacy claims that FDA approves antibiotics for use in food animals: disease treatment, disease prevention, disease control and growth promotion - as measured by the amount of feed needed to produce a pound of animal weight or increased rate of weight gain.

The first three uses – disease treatment, prevention and control – are considered to be therapeutic uses by FDA, the American Veterinary Medical Association (AVMA) and such international bodies as Codex Alimentarius and the World Health Organization (OIE). While critics of antibiotic use like to use the term "nontherapeutic" to refer to disease prevention, disease control and growth promotion, this term is not used nor recognized in national or international regulation.

Many assume in-feed uses equate to growth promotion, but this confuses the use with the route of administration. In fact, any of the four uses, including therapeutic, can be administered via feed or water, as that is under certain circumstances the only practical way to administer medication to large flocks or herds. In most cases, a veterinarian is involved in this process, recommending feed that is specifically formulated for the health management system used for the flock or herd.

How Antibiotics are Regulated

Veterinarians, Producers, and Animal health companies rely on a rigorous, efficient, predictable and science-based review process at the Food and Drug Administration's Center for Veterinary Medicine (CVM) to provide these products. The standard for the approval of antibiotics used in animals is the same as that for antibiotics used in human medicine: they must be shown to be safe and effective.



The rigorous review process and post approval monitoring systems in place are at the heart of a broad system of protections that ensure that all medicines, including antibiotics, are safe for animals and humans. Antibiotics for use in animals must meet all the same requirements as antibiotics used in humans, with two additional requirements: first, sponsors must show the meat, edible tissues, milk and or eggs from animals in which the medicine is used is safe for human consumption. Product sponsors have the burden of proof upon them to demonstrate the safety to the Agency. Second, beginning in 2003, CVM instituted Guidance for Industry (GFI) # 152, which

outlines a qualitative risk assessment process that is applied to all antibiotics approved for use in animals. This guidance process is designed to measure the risk of antibiotic resistant bacteria being transferred from animals to humans if the product is approved. Based on this risk, FDA makes decisions to either deny or approve the drug with certain restrictions to significantly reduce risk. Restrictions can include requiring a veterinary prescription, prohibiting extra-label use in certain species or restricting the antibiotic to individual animals. In most cases antimicrobial resistance monitoring is required post approval. The methodology is very conservative – meaning it is very difficult to get an antibiotic approved. Further, the guidance is sufficiently broad so that if new, previously unidentified or undescribed, resistant organisms or genes were to become of concern, the Agency can act swiftly to take this information into account. The existing guidance allows the Agency sufficient flexibility to allocate resources appropriately to changing issues of safety related to resistance emergence.

In response to concerns raised in the 1970's, FDA required sponsors to conduct tests to determine the potential for resistance to be selected in the animals and to be transferred to bacteria that could cause human disease. While the standards and science may have changed over the years, the safety of these products has been continually demonstrated as an ongoing exercise at FDA. Since there has been a greater availability of susceptibility data on marketed products, we believe that quantitative risk assessment is now the proper tool for making policy decisions about the safety of currently approved antimicrobials and is more appropriate than simply applying the tenets contained in Guidance 152. Published quantitative risk assessments, performed by both the Agency and individual product sponsors, have affirmed that the risks to human health from these antibiotics in animal feed under approved conditions of use are very low.

Recent FDA Actions

The FDA has proposed two initiatives to ensure the judicious use of animal antibiotics. In March, the Agency issued an Advance Notice of Proposed Rulemaking regarding the modernization of the Veterinary Feed Directive, which requires veterinarian involvement when antibiotics are administered in animal feed. And on June 28, the FDA issued draft guidance on the use of medically-important antibiotics in food-producing animals. Draft Guidance 209, *The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals*, had two specific recommendations: 1) the use of medically-important antibiotics in food-producing animals should be limited to uses necessary for assuring animal health, and the use for growth promotion are not judicious uses and 2) that the use of medically-important antibiotics in food-producing animals should be limited to uses that include veterinary oversight.

We look forward to collaborating with the Agency to help ensure that the process envisioned by these new initiatives will result in animal producers and veterinarians having access to the tools they need to protect the health of food producing animals. We appreciate that FDA has reached out to stakeholders for input on how to achieve their objectives. It is critical that stakeholders are involved to ensure that changes to the judicious use guidelines and the regulatory framework are carefully considered.

These recent initiatives further illustrate that FDA already has a great deal of authority to regulate the labeling and use of antimicrobials, and that it is willing to use it to ensure safe and judicious use of antibiotics in food producing animals.

In addition to the rigorous review process and the additional public and private risk assessments that have been conducted, there are other post-approval layers of protection to ensure the safe use of antibiotics.

Monitoring programs

USDA's Food Safety and Inspection Service monitor meat samples for the presence of antibiotic residues as a check on the observance of the withdrawal times set by FDA. It is very uncommon for FSIS to find an unsafe residue, an indication that products are being used according to label directions.

The National Antibiotic Resistance Monitoring System (NARMS) is a multi-agency program coordinated by FDA to monitor antibiotic resistant bacteria and allow for implementation of management and control measures if needed. The three agencies involved are:

- The USDA Agricultural Research Service (ARS), which analyzes *Salmonella* and *Campylobacter* isolates collected from carcasses and meat samples in the USDA FSIS HACCP/Pathogen Reduction Program for antibiotic resistance;
- The FDA, which monitors for resistant bacteria in retail meats;
- The Centers for Disease Control and Prevention (CDC), which collects isolates from public health laboratories to monitor for the emergence of antibiotic resistant enteric pathogens in humans.

To date, the animal and human arms of the program have produced eleven years of data representing over 19,000 *Salmonella* isolates from livestock and poultry carcasses and meats and 12,000 human *Salmonella* isolates, while retail meat testing was added later. Most bacterial species isolated from humans and tested for resistance against drug classes potentially related to animal usage have shown stable or declining resistance to most antimicrobials. Most of the multiple-drug resistance types, such as *Salmonella typhimurium* DT104 show stable or declining prevalence in both food animals and humans since 1996, according to an expert report issued in 2006 by the Institute of Food Technologists entitled "Antibiotic Resistance: Implications for the Food System."

While AHI strongly supports continued funding of the NARMS program, we would point out that there are inherent weaknesses in the sampling strategies that prevent the data from estimating a true national prevalence of resistance and yearly trends. The FDA Science Board has identified these weaknesses as well and has encouraged the agencies involved in NARMS to work to improve the data.[5]

Judicious Use Guidelines

Responsible or judicious use programs that are specific to different livestock species give veterinarians and producers specific guidelines to help them safely and properly use of antibiotics in their health management systems. Generally, these guidelines have been prepared collaboratively by FDA, CDC and veterinary groups. These guidelines help ensure there is no unnecessary use of antibiotics in animal agriculture. Others testifying today will provide additional detail on how these principles are used by veterinarians and producers.

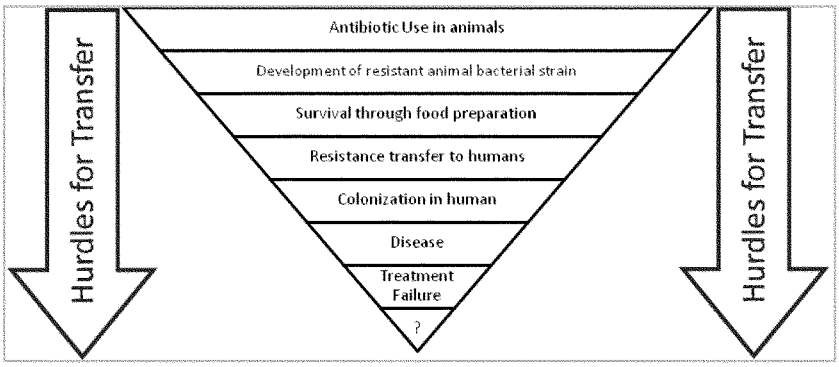
International Guidelines

Codex Alimentarius is responsible for protecting the health of consumers and ensuring fair practices in food trade. In 2007, Codex established an ad hoc Intergovernmental Task Force on Antimicrobial Resistance to develop guidelines for food safety risk analysis of antibiotics used in animals. The Codex Commission just last week, advanced draft guidelines to Step 5, meaning that the Task Force will likely be finalizing guidance in October 2010 for adoption as a Codex standard in 2011. International standards are important, because bacteria knows no borders and actions taken within the U.S. may not be as effective if there is not concerted international action. It is also important that the international community establishes a sound scientific basis for countries to assess the risk of antibiotic use. Otherwise, government regulators are left open to outside pressure to take overly zealous precautionary measures that may be unjustified and in the long term harmful to animal health and food safety.

Correlation Between Use of Antibiotics in Animals and Human Antibiotic Resistance

There is no question that antibiotic resistance is a serious public health threat. But resistance is not a single problem: it is a problem comprised of several different bacteria-drug combinations that must be examined individually to ascertain risk. For instance, some of the most widely recognized antibiotic resistance problems in humans are in respiratory tract infections and venereal diseases like gonorrhea. In neither of these cases is there any evidence that antibiotics used in animals are associated with these problems. In fact, in a survey published in 2000 a group of medical experts estimated the animal contribution to the overall human resistance problem is less than 4 percent.[6]

That small contribution was attributed to the potential for antibiotics used in food animals to contribute to resistance in certain bacteria which can be transferred from animal food products to humans. However, there is a chain of events from the "farm to the fork" that must be traversed by bacteria that develop resistance in animals as outlined in the accompanying chart:

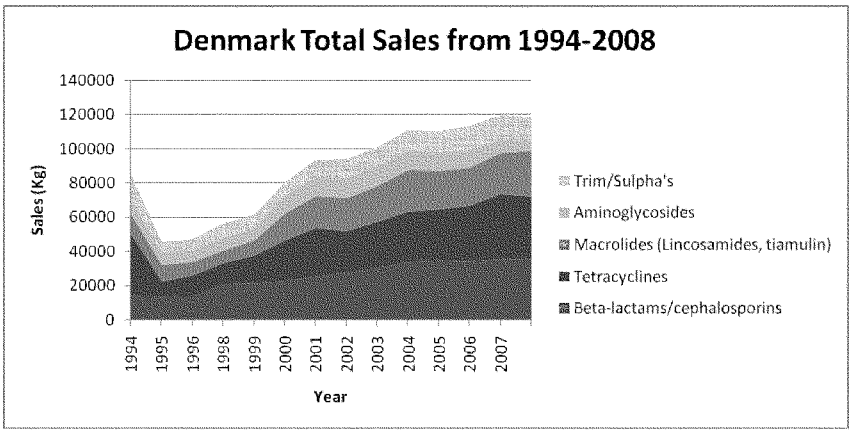


In order for resistance to happen, the antibiotic must be used in the animal, resulting in the selection of resistant bacteria in the animal. Those bacteria then must survive the slaughtering and processing of the animal. Remember, we have successfully reduced the number of bacteria -- both resistant and not resistant – that survive this process through the implementation of controls like HACCP. The bacteria must then survive the normal cooking process. If enough resistant bacteria survive to this point and are ingested in a large enough quantity, they can make an individual sick with a common foodborne illness. As you know, most foodborne illnesses are self-limiting – they resolve themselves in most cases without antibiotics being necessary. In the event that an antibiotic is necessary, the illness could be treated with the antibiotic that the bacteria is resistant to, and the treatment could fail, prolonging the illness.

While we know this can happen, the question becomes, how often does this happen and how severe are the consequences? The answer to this much-studied question is that it does not happen enough that we can find it and measure it. So, scientifically, we cannot say it does not happen, but we can say it is uncommon.

Danish Experience

The Danish experience provides a real world example of what happens when producers lose access to antibiotics. In the late 1990s, the European Union phased out one particular use --the use of antibiotics for growth promotion. Data from the Danish government, which you see on the accompanying chart, shows that use of antibiotics to treat disease has doubled since the ban.



This data, along with the discussion in the Danish report, clearly indicates the ban led to additional animal disease and death. The important question is: what impact did it have on public health? There is some evidence to indicate resistance declined in the animals and human s in certain bacteria. However, there is no evidence that this has resulted in reducing the public health burden of resistant bacterial infections in humans. The list of references at the end of my testimony includes published papers on the results of the ban.

Antibiotics Data

Critics have charged that we don't know how big the problem is because we don't have reliable data about the use of antibiotics in animal agriculture. However, it is important to note, that levels of antibiotic resistance are not correlated to the amount of use. Nonetheless, Congress has addressed the lack of data issue by requiring antimicrobial sales and distribution data to be reported to FDA under the Animal Drug User Fee Amendments of 2008. The ADUFA data collection requirements commenced this year, and our companies have complied. The FDA has indicated they will publish a report later this year.

Furthermore, Congress acted on this issue in the 2008 Farm Bill. That legislation contained an authorization for USDA's Agriculture Research Service to conduct additional research to study the development of antibiotic resistant bacteria in livestock on how judicious use principles can help producers use these products to protect both human and animal health.

Summary

In conclusion, antibiotics are vitally important to the health of our nation's livestock and poultry herds and flocks. Antibiotics are highly regulated and are used carefully by veterinarians and livestock and poultry producers. The many regulatory layers of protection that have been put in place allow us to safely use antibiotics to protect both animal and human health. The FDA regulatory process and risk assessment are the proper tools for making decisions about the use of these products. FDA has recently expressed concerns with antibiotic use in food animals; the industry is committed to working collaboratively with the Agency to address these concerns while assuring the availability of important animal health products to prevent, control, and treat animal disease.

Notes

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Ms. SCHAKOWSKY. Thank you.
Dr. Levy.

STATEMENT OF STUART LEVY

Dr. LEVY. Thank you. Mr. Chairman and members of the subcommittee, thank you for inviting me to testify on this crucial subject of antibiotic use in animal husbandry. I am Stuart Levy, a physician, research scientist and Professor of Molecular Biology, Microbiology and of Medicine at Tufts University School of Medicine in Boston. I also serve as President of the Alliance for Prudent Use of Antibiotics.

For more than 3 decades, I have been studying antibiotic use in animal husbandry and its effect on bacteria associated with animals, farm workers and their families and the environment in general. Throughout my career, I have noted the paradoxical nature of human engagement with antibiotics, hence the title of my book, the Antibiotic Paradox. On one hand, antibiotics cure disease, are miraculous. On the other hand, they select among their targets those which are resistant and make these drugs not effective.

My own research stretching back to the early 1970s has confirmed the broad environmental impact of antibiotic use, and I stress that. We performed the first and only prospective study of the effect of introducing antibiotic-, in this case, tetracycline-laced feed for chickens on a farm. By one week, almost all E. coli bacteria in the intestinal tracts of chickens were tetracycline resistant. By 3 months, the chickens and most of the farm dwellers were excreting E. coli not only resistant to tetracycline but to other antibiotics as well. We also demonstrated that low-dose non-therapeutic amounts of tetracyclines can in fact propagate bacteria resistant to the drug and other antibiotics at high levels. Resistant bacteria were found to move among animals and from animals to people.

Antibiotics are unique. They are societal and ecological drugs. Each individual taking an antibiotic whether animal or person becomes a factory producing antibiotic-resistant bacteria. Thus, there is a difference in the environmental impact when the same amount of antibiotic is given to one as opposed to a number of animals sharing that particular environment. In principle, fewer animals will be given antibiotics and for less time when antibiotics are used prophylactically as compared to growth promotion.

Mr. Chairman, we are not gaining ground in the struggle against antibiotic resistance. Antibiotics are continually misused and overused in both human medicine and animal medicine at great cost to our society in terms of human health and cost of health care. It is estimated that antibiotic resistance leads to more than $20 billion in hospital costs and up to $35 billion when society costs are included. Some progress has been made in encouraging more judicious use of antibiotics in human medicine but there has been precious little progress with respect to stemming the spigot of antibiotics flowing into animal agriculture.

In contrast, other industrialized nations have come to the same conclusion that many public health organizations around the world have, and that is that the use of antibiotics for growth promotion and feed efficiency must be curtailed. We can take some encouragement in the FDA's recent release of a draft guidance. We need to

move with greater urgency to stem the use of antibiotics in industrial animal production. Because most antibiotics currently approved for growth promotion are also approved for routine disease prevention, I have great concern that feeding large quantities of antibiotics non-therapeutically will continue, rendering meaningless any FDA guidance on eliminating antibiotic use for growth promotion.

Mr. Chairman and committee members, in view of the certainty in my opinion of the public health threat, the history of regulatory inaction and unyielding nature of the relevant industry, it is now clear that even a well-intentioned FDA is unable to overcome the influence of agribusiness. We have given moral persuasion, medical urgency, scientific study and voluntary guidance a chance and the situation has not changed. We can't wait any longer.

Legislation pending in this session of Congress, the Preservation of Antibiotics for Medical Treatment Act, would withdraw the use of seven classes of antibiotics vitally important in human health from food production unless animals are sick with disease or the use is needed for disease prevention without threat to human health. I urge this committee to move expeditiously to consider and approve this important legislation.

Thank you for giving me the opportunity to testify, and I will answer any questions.

[The prepared statement of Dr. Levy follows:]

TESTIMONY OF DR. STUART B. LEVY

President, Alliance for the Prudent Use of Antibiotics

Distinguished Professor of Molecular Biology & Microbiology and of Medicine
Tufts University School of Medicine

Before the Subcommittee ou Health of the
U.S. House Committee on Energy and Commerce

July 14, 2010

Mr. Chairman, I want to express my appreciation to the House Energy and Commerce Committee for convening today's hearing, for its ongoing work to help stem the crisis of antibiotic resistant bacteria and for inviting me to share my thoughts on these issues.

By way of background, my name is Dr. Stuart B Levy and I am Distinguished Professor of Molecular Biology and Microbiology and of Medicine, as well as the Director of the Center for Adaptation Genetics and Drug Resistance at Tufts University School of Medicine and Staff Physician at Tufts Medical Center. I also serve as President of the Alliance for the Prudent Use of Antibiotics (APUA), an international organization with members in over 100 countries and am Chief Scientific Officer of Paratek Pharmaceuticals. I am a Fellow of the American College of Physicians, Infectious Disease Society of America, the American Academy of Microbiology, and the American Association for the Advancement of Science. I am a past President of the 40,000-member American Society for Microbiology.

For more than three decades, I have been studying and following the issue of antibiotic use in animal husbandry and its effect on bacteria associated with the animals, on the farm workers and families, and the environment in general. Throughout my career, I have been happy to appear before Congressional panels like this one to share my views on the science and solutions surrounding these issues. I vividly recall testifying in December 1984 before the House Subcommittee on Investigation and Oversight of the Committee on Science and Technology on antibacterial resistance and the data showing spread of resistant bacteria among animals and among animals and people.

In that testimony and throughout my career, I have noted the paradoxical nature of human engagement with antibiotics (1). On the one hand, these miraculous drugs are pillars of modern medicine, helping us to manage and prevent dangerous bacterial infections and save lives. On the other hand, the widespread use – and misuse – of antibiotic drugs has spawned the evolution of life-threatening bacteria that render our current antibiotics useless.

In 1975-76, my research group performed the first, and I believe only, prospective study of the effect of introducing antibiotic-laced feed on a farm (2). We established a family farm about 40 miles West of Boston. We introduced chickens, hatching from eggs laid from pathogen-free hens, and separated them into two groups of 150 chickens each. One group received low dose antibiotic-laced feed (oxytetracycline (100g/909kg)), and one did not.

The findings were striking. Within 24-48 hours, the chickens given the oxytetracycline-laced feed began to excrete tetracycline-resistant *E. coli*, a common bacterium in the feces of chickens,

people and other mammals. The control group did not. By one week, almost all *E. coli* in the intestinal tracts of the antibiotic-treated chickens were tetracycline-resistant.

As time continued on this single low-dose antibiotic, the bacteria in the feces of the chickens began to acquire more and more resistances. By 3 months, the chickens were excreting *E. coli* resistant not only to tetracycline, but also to sulfonamides, ampicillin, streptomycin and carbenacillin.

Most striking was that the farm family, as compared to the control group of neighborhood farm dwellers – none using antibiotics – also showed an increasing number of fecal *E. coli* resistant to multiple antibiotics.

This study demonstrated the ecologic and environmental impact of an antibiotic, in this case low-dose antibiotics, on the animals housed in the farm and on the farm dwellers themselves. It answered one principal question at that time: that low-dose nontheraputic amounts of antibiotics can, in fact, select for, and help propagate, bacteria resistant to the drug at high levels.

The study also resulted in other important findings. There were increased numbers of multidrug resistant bacteria among people on the farm, even though they were not taking antibiotics. Of note, transfer of *E. coli* from the chickens to the farm workers was also observed (3).

In subsequent studies, we haved demonstrated that even in the absence of an antibiotic, resistant bacteria will move from animal to animal, in this case from bull to calf, to pigs to chickens, presumably through the air (4). Additionally, we demonstrated the presence of resistant bacteria on flies. In the study, it was clear that farm workers could pick up the biochemically-marked *E. coli* that was initially put into the bull, where it remained in their intestinal tracts at a detectible level for several weeks. Thus, there is no containment of antibiotic or antibiotic resistant bacteria in the farm environment.

As you can see, Mr. Chairman, much of my personal energy and professional endeavors have been given to better understanding the causes of antibiotic resistance and advancing solutions to this growing threat to human health.

Drawing on that experience, I regret to report to this Committee that we are not gaining ground in the struggle against antibiotic resistance and all of us – you, me and your constituents – are at ever greater risk of contracting a resistant bacterial infection and even one that is untreatable.

- Antibiotics continue to be misused and overused on a massive scale in both human medicine and animal agriculture; and
- There is a dearth of activity in large pharmaceutical firms to develop new drugs that can best antibiotic resistant bacteria. Fortunately, the void has been filled by work performed in small biopharmaceutical companies like the one I co-founded, Paratek Pharmaceuticals.

Some progress has been made in developing protocols and encouraging more judicious use of antibiotics in human medicine. There is awareness of the crisis and our public health agencies have developed protocols for promoting proper use of antibiotics by doctors and patients alike.

But there has been precious little progress with regard to stemming the spigot of antibiotics flowing into animal agriculture. Indeed, the Food and Drug Administration has attempted on several occasions to initiate prudent steps for curtailing the misuse of antibiotics in industrial agriculture, only to be thwarted by powerful industry interests, which have questioned the science and mobilized Congressional allies at every step of the way.

These efforts have been undertaken despite a mountain of domestic and international scientific evidence demonstrating the linkages between the use of antibiotics in animal agriculture and the emergence of bacteria resistant to antibiotics of critical importance to human health and to the frequency of resistant strains of bacteria in human beings.

There are a number of common concepts in the antibiotic resistance field that we have learned over the years, which I think are relevant when in evaluating the nontheraputic use of antibiotics in animal husbandry (5).

One, antibiotics are "societal drugs." Their use in one individual can affect the level of resistance and the presence of resistant organisms in other individuals sharing the same environment. An excellent demonstration of the concept came from Dr. William Cunliffe's dermatologic group in London, which showed that those sharing the household with patients treated for acne picked up and began to shed *staphylococci* from their skin that were multidrug-resistant, as were the bacteria found on treated patients. This was not true among households where an antibiotic was not used (6).

Secondly, as discussed earlier, antibiotics have an environmental impact. They are ecologic agents – they can change the bacterial environment, largely from drug-susceptible organisms to resistant ones (7). Moreover, these do not have to be therapeutic amounts of antibiotics; nontheraputic low-dose antibiotics have a similar profound ecologic effect. Furthermore, an important finding was that the length of time on the antibiotic (tetracycline) selected bacteria with resistances to more than the tetracyclines. In animals, long term use of the single antibiotic led to multidrug resistant bacteria. This phenomenon has been seen among women taking tetracycline for treating urinary tract infections. In these patients, 1-to-2-week-use led to multidrug resistant *E. coli* in their intestinal tracts (8). This is critical when we begin to discuss the total time of antibacterial treatment of animals whether it is for growth promotion, for disease prophylaxis, or for therapy. The amount of time on the antibiotic can influence the numbers of resistances that appear in the bacteria associated with these animals.

Third, a point that I think is missed often, is that the total amount of antibiotic does not tell us enough about what is happening in that environment. We need to know about the distribution of the antibiotic. For example: You have 100 grams of antibiotic, and you give all of it to one animal. That animal becomes the single producer of resistant bacteria, which it can shed to the environment. On the other hand, if you give those 100 grams to 100 different animals, you now have 100 times more "factories" of resistant bacteria that are being propagated by the selection of the antibiotic. This point, I stress, is critically important in evaluating the data when amounts are only presented in total numbers, in grams, in kilograms. We need to know how many animals are being affected. There is no doubt that with billions of animals being treated with antibiotics in our country, as opposed to millions of people sporadically, that there are many more "factories" of antibiotic resistant organisms among the animals, then the people, and especially in those instances where the therapy is prolonged for weeks and at less-than-therapeutic amounts.

APUA has been following this issue for some time. We have looked at the different routes of transfer of antibiotics and antibiotic resistant bacteria, as shown in the attached figure. At each step of the way, there are data demonstrating the means of transfer of either the antibiotic or the resistant bacteria, or both. Water downstream from farms has been found contaminated with antibiotics leeching through the ground. It is critically important to look at how the drug and the amount of the drug is being given in water or by injections. If it is given in a way that is not contained, there is much more environmental contamination. So if one can focus on the amount of drug, how it's being delivered, and how it's being distributed – that is, the vehicle and how many individuals (animals, people, plants) are being given the antibiotic, one can appreciate better how to control the unwanted consequences of antibiotic use (9).

Several years ago, APUA put together a stakeholders' group that came up with recommendations for improving antibiotic use in the raising of farm animals. It was concluded that antibiotics for nontheraputic use should be eliminated, since the benefit was unclear and did not merit the practice. On this point it is noteworthy that there are no current studies to show that a growth promotion effect still exists.

Other industrialized nations, most notably in Europe, have come to similar conclusions and have taken steps to curtail the use of antibiotics for the purpose of growth promotion and feed efficiency. But the United States lags behind and has done almost nothing to curtail non-therapeutic uses.

In view of this history, it was very encouraging that the FDA announced on June 28, 2010 its draft guidance to industry on the use of antimicrobial drugs in food-producing animals.

The FDA is to be applauded for stating boldly and accurately that: "Overall, the weight of evidence to date supports the conclusion that using medically important antimicrobial drugs for production purposes is not in the interest of protecting and promoting the public health."

The FDA's draft guidance establishes a number of key foundations for the future: first, that there is broad agreement that antibiotics should be deployed under the guidance of veterinarians to treat sick animals; second, that antibiotic use for growth promotion and feed efficiency is not judicious, is contrary to human health and should be stopped; and third, that antibiotics may be used on a prophylactic basis for short-durations with at-risk animal populations under the direction of a veterinarian. These are important building blocks for forging consensus between public health and agriculture interests in the future.

There is less consensus around the use of antibiotics in generalized prevention, where antibiotics are used in the absence of specific animal health risks to guard against infections that might otherwise be prevented with additional sanitation measures and less crowded conditions. There is an absence of studies to show the scientific basis for prophylaxis and the time and dose required. Such studies have improved prophylaxis use in human medicine, most notably in surgery.

The FDA's draft guidance is a welcome step and reflects the kind of foresight and wisdom I've waited years, even decades to hear from this institutional guardian of animal and public welfare. Nonetheless, the FDA's recent action represents only voluntary guidelines that would take many months, perhaps years to finalize. Even if finalized as voluntary guidance to industry, the reality is that agribusiness has fought efforts to curtail overuse of antibiotics every step of the way and

there is no basis for confidence that industry will do anything but dodge and challenge the FDA's guidance. Because most antibiotics currently approved for growth promotion are also approved for routine disease prevention, I have great concerns that industry will continue feeding massive quantities of antibiotics non-therapeutically, rendering meaningless the FDA guidance on eliminating antibiotic us as growth agents.

Mr. Chairman and Committee Members, in view of the urgency of the public health threat, the history of regulatory inaction, and the unyielding nature of the relevant industry, it is now clear that even a well-intentioned FDA is unable to overcome the power and influence of agribusiness. We've given moral suasion, medical urgency, scientific study and voluntary guidance its chance and the problem has only grown worse. We can't wait any longer. Congress must act.

I applaud you for convening today's hearing and for developing a Congressional record on the evidence of this significant challenge. But the evidence is clear and compelling and it is time to move from educational hearings to legislative mark-ups.

Legislation pending in this session of Congress, the Preservation of Antibiotics for Medical Treatment Act (PAMTA, H.R. 1549, S. 619), would withdraw the use of seven classes of antibiotics vitally important to human health from food animal production unless animals or herds are sick with disease or unless drug companies can prove that their nontherapeutic use is needed for disease prevention and only at high risk times in their rearing and does not represent the threat to human health. This is a sensible and effective approach toward curtailing the use of antibiotics in industrial farming and I urge this Committee to move expeditiously to consider and approve this important legislation.

Thank you for your consideration of my testimony and I would be happy to answer any questions you may have.

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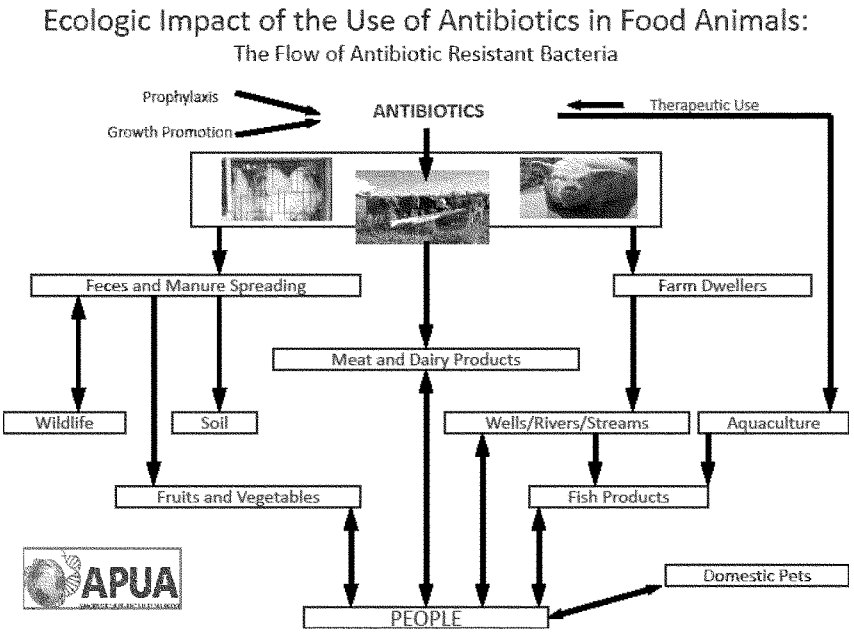
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Figure:


Ecologic Impact of the Use of Antibiotics in Food Animals:
The Flow of Antibiotic Resistant Bacteria
Prophylaxis
Growth Promotion
ANTIBIOTICS
Therapeutic Use
Feces and Manure Spreading
Farm Dwellers
Meat and Dairy Products
Wildlife
Soil
Wells/Rivers/Streams
Aquaculture
Fruits and Vegetables
Fish Products
APUA
Domestic Pets
PEOPLE

Ms. SCHAKOWSKY. I want to thank all of our witnesses. As is obvious, I guess, Mr. Pallone had to go to yet another committee that he is on where they are voting and so he won't be able to return.

I have some questions that I want to ask but I also want to let you know that we have a whole bunch of questions that I fear will not be asked and therefore we will get them to all of you and would appreciate very much your answers in writing later.

Mr. SHIMKUS. Madam Chairman, can we also ask, it wasn't done, I think, a UC that all members' statements can be submitted for the record?

Ms. SCHAKOWSKY. That all members' statements can be submitted for the record, without objection so ordered.

Mr. SHIMKUS. Thank you.

Ms. SCHAKOWSKY. I want to give a special thank you to Dr. Henriksen for coming from Denmark, and I wanted to give him the opportunity at this hearing to answer some questions, because there has been a lot of discussion about the Danish experience. We have seen articles and heard testimony claiming that even though you eliminated the use of antibiotics for growth promotion, you ended up using more antibiotic than you had before because all the animals got sick. That is what we are hearing. And in fact, in the testimony of the American Veterinary Medicine Association, Dr. Hoang states and Dr. Singer as well that antibiotic use went up between 1998 and 2008. So can you clarify for us exactly what the situation has been with regard to antibiotic use in Denmark? And as part of that, can you tell us what steps you took to reduce antibiotic use and what impact each step has had on the use of antibiotics?

Dr. HENRIKSEN. Yes, I will try to answer your questions, all your questions. It is correct that after the ban the consumption of therapeutic antibiotics has been increased but in the same period the pig production has been increased too, and if you see my fact sheets on page 10, you can see figure 1 which both has the antibiotic usage in all types of animals and the number of pigs produced, and in that period from 1998 to 2008, you can see an increase in the therapeutic use of antibiotics but an almost similar increase in the number of pigs produced in Denmark. You can put it another way, that is to calculate how many milligrams per kilo pig produced in Denmark, and you can have the data before the ban. Before the ban in 1994, the total use of antibiotic growth promoters and for therapeutics were 99 milligrams per kilogram of pig produced, and even in 2008 the total consumption was 49 milligrams per kilogram pig produced. That is, we have reduced the total usage of antibiotic per kilogram pig produced from 99 to 49 milligrams. That is a 50 percent reduction.

It is correct as stated by many U.S. observers that the disease situation has changed in Denmark. Diseases come and go in humans and animals, but if you look at the fact sheet on page 14, you can see the mortality in weaners, the mortality since 1993 to 2003, 2004 has been increasing from about 2 percent to almost 5 percent, but since 2004 the mortality in weaners has decreased almost to the level from 1992–1993. So in that respect to mortality in weaners, the more focus of disease in Danish pig production cannot be released by the mortality figures. If you compare to the mor-

tality in finishers in figure 7 on page 14, you can see that the mortality has been varying little during the 1992 to 1997, 1992 to 2007, but the mortality is between 3 and 4 percent. So there has not been any significant impacts on mortality neither in weaners nor in finishers.

I would like to add on the previous page on the fact sheet, page 13, figure 4, this is the productivity as we express it in Denmark, number of pigs produced per sow per year, and you can see from 1992 to 2006, 2007, the number of pigs per sow per year has been increasing from 20 to more than 22 pigs per sow per year. That means that during this phasing out of growth promoters has been increasing production, but I would of course admit in some farms you see severe disease problems, and this is the task for a trained veterinarian to deal with the specific problem in specific farms whether it should be a vaccination schedule, prophylactic changes in the environment, new ventilation system, better feed quality and so on, maybe prolonged weaning age from 3 weeks to 4 weeks, or treatment with antibiotic. So that I think most of the questions I answered.

Ms. SCHAKOWSKY. Let me just then underscore and make sure that this is correct, that the total antibiotic consumption in food-producing animals has been reduced by about 40 percent from the mid 1990s until today. So we are talking about total consumption is just almost in half or about 40 percent. Is that correct?

Dr. HENRIKSEN. That is correct when you compare the total use of antibiotic growth promoters and therapeutic use in the end of 1997–98 to 2008, yes, that's correct.

Ms. SCHAKOWSKY. Thank you. I appreciate your being here and I appreciate your testimony.

Mr. Shimkus.

Mr. SHIMKUS. Thank you, Madam Chairman.

But I will say from ban until now, therapeutic use has gone up, and that—and you are shaking your head, which I think that means yes. We do appreciate you coming a long way.

Madam Chairman, and this has been addressed with the staff for submission to the record a statement from the pork producer, if you would——

Ms. SCHAKOWSKY. Without objection, so ordered.

[The information was unavailable at the time of printing.]

Mr. SHIMKUS. Thank you, Madam Chairman.

The other thing I want to—I need to highlight some stuff going back to the previous panel and the third chart I didn't get a chance to talk about. I think the issue—I just want to get it on the record that the United States and Canada had pathogen reduction regulations during this time and the issues of voluntary withdrawal too. So there is more to be said by charts that unfortunately we didn't have time to pursue that with the previous panel because of time.

Another thing I want to make sure to put on the record, and this is from the D.C. area, that there is a huge price discrepancy between food products that are antibiotic-free and conventional price, and there is a list of 10 products here and it goes from anything from 141 percent to 20 percent change in retail prices. So another thing to place on the table is the cost of basic food products from beef to eggs to you name some of the issues.

Also, the reduction in Danish swine farms from the passage of legislation from 12,500 to 3,500, and for my friend from Denmark, the United States is the number 1 pork-producing country in the world. He knows that. I think it is a percentage of what is exported based upon what is consumed. But I would say second is the EU followed by, I don't know if it is Canada or Brazil, but this is a major industry in the United States. It is a major industry in my Congressional district, and that is why we want to make sure that science is addressed because we are concerned about antibiotic issues. We have had hearings. But we want to make sure that again that we don't do more harm than good. And I appreciate the various opinions and the issues on risk because healthy animals should grow bigger. I mean, if you are sick, you are not going to grow. If you are healthy, you do grow.

We just passed a health care bill that said preventative—let us make sure we keep Americans healthy because of the high cost in taking care of sick people, but here we are going to flip the charts. We are going to turn it upside down. We are going to say let us don't keep the animals healthy, let us do therapeutic antibiotics when they are sick.

Dr. Carnevale, I have two questions, because we heard from a lot of the panelists both here and then also on the first panel that there is unequivocal evidence, and it reminds me of the climate change debate, that the science is settled. Well, I think the American public understands that the science is not settled. Is there unequivocal evidence that there is a connection between the use of antibiotics in animals and connect them to human health?

Dr. CARNEVALE. Well, as many have said today, this is a very complicated issue. I would say there is not unequivocal evidence that the use of antibiotics in animals, particularly those used in animal feed, are directly responsible for human health impacts, and human health impacts has been kind of loosely defined here, but I would certainly think that the most key human health impact would be failure of the treatment of a disease.

Mr. SHIMKUS. Yes, and let me—my time is very limited and I want to be respectful of my colleagues. And the animal feed issue is different than what the Danish experience was in the use of antibiotics. I don't want you to elaborate.

I want to follow up. My second question is, the FDA role. The FDA role is to make sure they approve drugs for animals and for humans. Now, when they say this antibiotic is good for use in animals, do they also look at its possible risk for human consumption through the process? Do they have to consider the effect on human health?

Dr. CARNEVALE. Yes.

Mr. SHIMKUS. So when the FDA says it is OK, it is not only saying it for the animal, it is saying it for human health and consumption?

Dr. CARNEVALE. Absolutely. They have a mandate to approve drugs safe and effective, which means safe to the animal, safe to humans and safe to the environment.

Mr. SHIMKUS. My time is expired. Thank you, Madam Chairman.

Ms. SCHAKOWSKY. Thank you.

I wonder if you would mind if I just follow up with Dr. Henriksen, just find out what the Danish experience was on the cost of production after the ban. I don't know if——

Mr. SHIMKUS. No, we talked and I will be happy as long as our colleague down there is fine.

Ms. SCHAKOWSKY. Just a quick question. Was there any impact on the cost of production after the ban or the cost to the consumer after the ban?

Dr. HENRIKSEN. The prices in the shops have not been increased due to this ban. I don't have any data available with me about the production costs for the farmer.

Ms. SCHAKOWSKY. Thank you.

Dr. HENRIKSEN. I can present it to you if you want.

Ms. SCHAKOWSKY. Thank you.

Congresswoman Christensen.

Mrs. CHRISTENSEN. Thank you, Madam Chair, just a few questions.

Dr. Hoang, the AVMA, I understand, suggests that the current FDA approval process for antibiotic use in food animals is sufficiently strict to protect human health but the FDA doesn't apply a standard regarding antibiotic resistance retroactively to drugs that were approved maybe decades ago. So what is the AVMA's position? Should we reevaluate the safety or not of already approved drugs?

Dr. HOANG. The AVMA is supportive of reevaluation of the drugs that have been previously approved, but I might also add that the FDA does have the authority to withdraw a drug if they find that there is an imminent human health hazard, which they have not done so.

Mrs. CHRISTENSEN. Thank you.

Dr. Levy, why do you think the United States has yet to follow the example of other industrialized nations in limiting antibiotic use in meat production? Is it because the scientific basis for action is questionable? It seems to me there is a lot of evidence. I don't think the bacteria behave much differently here than in Europe, so what do you think the reason is?

Dr. LEVY. That is exactly what I was thinking. It has bothered me a lot as I go out to teach about how to use antibiotics that Europe, I think, is ahead of us by eliminating this major source of resistant emergence. Why? It is much more difficult in this country to get this ban. I had preferred all along in my career that it would be more voluntary and that you wouldn't need a legislative ban, but I have been disappointed.

But anyway, all that being said, as we know, the Europeans looked at the data and with one fell swoop they said precautionary principle, we eliminate this use. I think the scientific data is clear, and I am a scientist and I have looked at the data, and the APUA has actually put out a few years ago an evaluation of this whole prospect with stakeholders and all agreed that this is no longer needed. First of all, we don't even know if growth promotion is really working. If it is prophylactic, let us call it prophylactic. And as I said in my statement, there is a big difference in terms of the selection of the numbers of animals that we get for growth promotion, which is everyone, whether healthy or not, versus prophy-

laxis, which in human medicine, look at what we do with surgery. We eliminated all that extra antibiotic and we gave a dose before and a dose or two after. Why aren't we doing that with animals? Where are the studies? If we call it prophylaxis, show me that it is prophylaxis. Show me what—I mean, a spade a spade. What is it? And so I think it is a different, should I say culture, but I don't think that anyone—there are plenty of us in the United States that agree with the European decision.

Mrs. CHRISTENSEN. And I noted Dr. Hansen in her statement—I don't have a question for you but I know that you said that even in 1977, that is where I got the point I made in my opening statement, that the evidence was significant but we did not allow FDA to apply a ban. Is that correct?

Dr. HANSEN. Yes, ma'am. I would certainly agree with that. I think that we certainly don't lack the science at all. We certainly have—this is just a representative portion of the science that we have. We may lack or we may have at least up until this point with all these hearings may have lacked some of the political will.

Mrs. CHRISTENSEN. Thank you.

Dr. Carnevale, how does AHI justify opposing significant reductions in antibiotic use in food animals when such overuse ultimately helps to contribute to the demise in your products' ability to treat both human and animal disease? Aren't you sacrificing long-term financial well-being, not to mention public health, in favor of short-term profit in this case?

Dr. CARNEVALE. If I understand the question, you are saying why do we oppose reducing antimicrobial use. I don't think AHI has ever said that. I think what our position is is that these products have been approved as safe and effective by the FDA

Mrs. CHRISTENSEN. Safe and effective for treatment.

Dr. CARNEVALE. Safe and effective for all the claims on the label.

Mrs. CHRISTENSEN. From growth——

Dr. CARNEVALE. They have been approved as safe and effective for growth promotion, disease prevention, disease treatment and disease control, whatever is on the label.

Mrs. CHRISTENSEN. Well, FDA has issued some guidelines now regarding——

Dr. CARNEVALE. Yes.

Mrs. CHRISTENSEN. Does AHI support the guidelines that FDA——

Dr. CARNEVALE. We welcome the opportunity to work with the agency on their concerns about it. We clearly understand that they do have a concern about the way these products have been marketed for many years over the counter. We do understand they have a concern for the growth promotion claims. I don't want to prejudge the situation. I simply want to say that our companies are committed to working with the agency to try to address those concerns, and if there are alternatives that we can come up with for growth promotion claims, I am sure our companies will be more than happy to pursue that track.

Mrs. CHRISTENSEN. And are your companies——

Dr. CARNEVALE. Yes, we really want to work with the agency on this.

Mrs. CHRISTENSEN. Are your companies willing to report on the sale of medicines, drugs for animal use?

Dr. CARNEVALE. In fact, they are required to now under the Animal Drug User Fee Act. In fact, our companies have all submitted those reports to the FDA as of the end of March 2010. So yes.

Mrs. CHRISTENSEN. Thank you, Madam Chair.

Ms. SCHAKOWSKY. Well, that concludes all the questioning. I really thank you for your patience today, for staying with us all afternoon. In closing, I want to remind members that you may submit additional questions for the record to be answered by the relevant witnesses. The questions should be submitted to the committee clerk within the next 10 days. The clerk will notify your offices of the procedures.

And without objection, this meeting of the Subcommittee is adjourned. Thank you.

[Whereupon, at 5:55 p.m., the Subcommittee was adjourned.]

[Material submitted for inclusion in the record follows:]

U.S. Representative Kathy Castor
Committee on Energy and Commerce – Subcommittee on Health
Hearing: "Antibiotic Resistance and the Use of Antibiotics in Animal Agriculture"
July 13, 2010

- Thank you Mr. Chairman for convening the third hearing in our antibiotic resistance series.

- This afternoon's focus is critical – looking at ways to reduce antibiotic resistance by cutting down on non-judicious use of antibiotics in farm animals may prove to be vital to combating the growing problem of antimicrobial resistance in humans.

- It is clear that we need a comprehensive strategy to address antimicrobial resistance in humans, as resistant infections cause approximately 90,000 deaths each year and account for up to $26 billion a year in additional health care costs including hospitalization of infected patients for weeks or even months at a time.

- Our strategy must include an assessment of the use of antibiotics in farm animals.

- We must also take a closer look at the reasons that we are light years behind other nations, such as Denmark, in our effort to cut back on non-judicious use of antibiotics in animals.

- Here in the U.S., Salmonella bacteria are considered a norm for uncooked chicken and raw eggs.

- We promote the need to use everyday household disinfectants to keep families safe from bacteria frequently found in two of the most common foods.

- But, most Americans would be surprised to learn that Salmonella bacteria incidence in chickens can be prevented and is not innate. In Denmark, the incidence of Salmonella bacteria in poultry is 0-2%. Ironically, a problem that is so common in the U.S. that it is rarely considered a problem is almost non-existent in Denmark.

- Further, Norway is now the most infection-free country in the world after the implementation of an aggressive program to cut back on overuse of antibiotics in humans.

- Again, other nations are light years ahead when it comes to addressing this issue – one that we could have taken seriously many years ago.

- The notion that pumping farm animals with antibiotics can lead to overexposure to certain drugs during human food consumption is nothing new – it has been asserted for decades – yet there has yet to be a concerted effort to put a stop to it. It's time to get to the bottom of it.

- I am proud cosponsor of HR 1549, the Preservation of Antibiotics for Medical Treatment Act, which many other members of this Committee support. This legislation, introduced by Congresswoman Louise Slaughter of New York, would ban farm use of drugs that are critical to fighting human infection unless the animals are ill.

- I hope that today we can look closely at the concerns addressed in H.R. 1549.

- Again, thank you Mr. Chairman, and I look forward to hearing from our witnesses.

Opening Statement
Honorable Ranking Member Joe Barton
Subcommittee on Health
Hearing on "Antibiotic Resistance and the Use of Antibiotics in Animal Agriculture"
Wednesday, July 14, 2010 – 2:00 PM

Mr. Chairman, I would like to welcome the witnesses to the hearing and thank them for testifying today.

This is the third hearing we are having on the subject of antibiotics. Today, we will discuss the use of antibiotics in animal agriculture. In reviewing the testimony, it is clear that the federal government, veterinarians and producers are doing a great deal to ensure that antibiotics are being used safely.

The Food and Drug Administration, the Centers for Disease Control, and the Department of Agriculture are

conducting monitoring programs to track the development of antibiotic resistance. Veterinarians and producers have adopted and implemented judicious use programs to ensure that antibiotics are safely and properly used. The FDA has implemented a stringent approval process for animal drugs.

I understand that the FDA recently released a new guidance document in which it indicated that it would like to ban certain uses of antibiotics in animals. From what I understand, this ban could have some serious consequences for both public health and jobs. I would like to know more about why the FDA has proposed this major action at this time and what data serve as the scientific foundation for taking the proposed action.

I also want to note that this is our third hearing on antibiotics even though the Majority has yet to hold one hearing on how the President's new health care law is being applied to the American people. Last week, President Obama decided to appoint a new Administrator of the Centers for Medicare and Medicaid Services (CMS) through a recess appointment, thereby bypassing the constitutionally prescribed process of Senate confirmation.

I think the President's surprise decision to avoid the normal public examination of a nominee is another problem on top of the problems being generated almost daily by his health care law. Dr. Berwick has now taken an important jobwithout Congressional approval. The American people do not even know how Dr. Berwick intends to implement Obamacare, and this is wrong. For example, Congress and

the people have every right to know how Dr. Berwick will implement the $575.1 billion in Medicare cuts before he begins the cutting. People also have a right to know how Dr. Berwick will cut $145 billion from the Medicare Advantage program and who will lose their plans because of his decisions.

Dr. Berwick also will be in charge of implementing an unprecedented expansion of the Medicaid welfare program. Obamacare expands enrollment in this welfare program to more than 90 million people, and there will be an increase in spending of nearly 90% during the 2014-2019 period alone. Dr. Berwick and the Obama Administration owe the country an explanation of what they're up to.

Dr. Berwick's previous public statements suggest that he believes that the government should be the ultimate arbiter on the medical care that patients receive and that rationing is a legitimate function of government-supervised health care. Given the power of the Medicare and Medicaid Administrator and the concern regarding Dr. Berwick's seemingly radical opinions, this Committee needs to invite Dr. Berwick to testify at the earliest opportunity so he can speak for himself and clear the air. We need to know the direction Dr. Berwick intends to take his new agency and our nation's health care system.

Thank you, Mr. Chairman. I yield back the balance of my time.

BLUNT STATEMENT FOR E&C SUBCOMMITTEE ON HEALTH

July 14, 2010

Mr. Chairman,

Thank you for holding this hearing regarding antibiotics and animal agriculture.

As we have discussed in previous hearings, antibiotic resistance is a major concern for both human and animal health. Both doctors and veterinarians should always prescribe only what is essential to ensure that antibiotics are not used unnecessarily. I have met and spoken with many farmers and animal producers in my district on a regular basis. I know they have the utmost respect for antibiotics and seek to use them only when necessary to help maintain the health of their animals. They work in close consultation with their veterinarians because healthy animals are the first step in food safety.

Currently, the FDA must approve all medications administered to food-producing animals. These antibiotics undergo a stringent approval process. Recently, the FDA released new draft guidance regarding the judicious use of antibiotic drugs in food-producing animals. I hope the FDA will work closely with all stakeholders and listen to their comments, as they

move forward with finalizing Guidance 209. We should not restrict or reduce access to the tools that our farmers need to keep their animal populations healthy, as this would have a direct effect on human health.

We should also make sure to take into account the experiences of other countries when determining new guidelines. In 2000, Denmark put into place a ban on the use of antibiotics for growth promotion for cattle, pigs and broilers. Since then, the country has seen an increase in the instance of death and disease in their swine herds. Their producers have also had to use increased amounts of antibiotics used to treat their animals. As we consider policies that govern the use of antibiotics in animal agriculture, we must rely on science-based findings to make sound determinations.

I look forward to working with the chairman and my colleagues on the subcommittee regarding this issue.

Opening Statement
Congressman John Sullivan
Subcommittee on Health
House Energy and Commerce Committee
Antibiotic Resistance and the Use of Antibiotics in Animal Agriculture
July 14, 2010
2123 RHOB

Thank you for holding this hearing today to examining antibiotic resistance and the use of antibiotics in animal agriculture.

Antimicrobial drugs have been used in medicine for over 50 years and they have yielded tremendous benefits for public health and animal health.

In June, the FDA released new draft guidance about antimicrobial drugs and their use in food producing animals indicating that use of such antimicrobials for "production purposes" such as promoting growth and improving "feed efficiency" represents an **injudicious** use of such drugs.

There is much debate about whether antibiotic resistance bacteria can develop in animals and transfer to humans. As we examine this issue, it is important to note that there are no conclusive U.S. peer-reviewed studies indicating a link between animal antibiotic use and human

health. Further study is necessary and I fear that the FDA is going too far and too fast on this critical economic and food safety issue. It is vital that we challenge the scientific rational for the FDA's guidance and I am concerned that federal public health regulators are starting down a road that will inevitably lead to restricting the antibiotics that farmers and ranchers can use without evidence to support increased federal regulation in this area.

In addition to the FDA guidance, legislation has been introduced this Congress mirroring the FDA guidance that will ban the use of anti microbial drugs in animals. We need to be careful because such a ban could have serious economic and food safety consequences for our nation. I've heard that adopting such a ban would cost U.S. pork producers $1.1 billion alone, which would undoubtedly raise the cost of food while doing little to benefit public health.

I look forward to hearing the testimony from our witnesses today and I yield back the balance of my time.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Centers for Disease Control
and Prevention (CDC)
Atlanta GA 30333

July 13, 2010

The Honorable Frank Pallone, Jr.
Chairman
Subcommittee on Health
House Committee on Energy and Commerce
Washington, D.C. 20515

Dear Chairman Pallone:

Please find attached written responses to questions for the record from the Subcommittee's April 28 hearing on antimicrobial resistance. These responses provide additional detail on the strong scientific evidence of a link between antibiotic use in food animals and antibiotic resistance in humans.

There are multiple North American studies describing how:

- Use of antibiotics in animals results in resistant bacteria in food animals
- Resistant bacteria are present in the food supply and transmitted to humans
- Resistant bacteria result in adverse human health consequences (such as increased hospitalizations)

In addition, a strong body of evidence from Europe demonstrates that antibiotic use in animals is linked with antibiotic resistance in humans. Multiple studies looked at the effects of the Danish ban on non-therapeutic use of antibiotics in food animals. We have thoroughly reviewed these studies and have found them to be well-designed and rigorous, and to establish a clear link between antibiotic use in animals and antibiotic resistance in humans.

I appreciate this opportunity to restate my conclusions from the April hearing, and provide you additional detail. This opportunity is particularly important because some discussion at the hearing has been mischaracterized. To be clear, the Centers for Disease Control and Prevention (CDC) finds that there is a compelling body of evidence to demonstrate this link, as summarized above, in my April testimony, and in the attached responses to questions for the record. I am pleased that the Subcommittee is holding another hearing in its series on this important issue, and that Dr. Ali Khan will be able to represent CDC to further elaborate on this evidence regarding the relationship between antibiotic use in food animals and antibiotic resistance in humans.

CDC remains committed to working with Congress and our colleagues at the Department of Health and Human Services and the U.S. Department of Agriculture to identify the best ways to address the health risks posed by antibiotic resistance.

Sincerely,

Thomas R. Frieden, M.D., M.P.H.
Director, CDC, and
Administrator, Agency for Toxic Substances
and Disease Registry

Cc: Rep. John Shimkus, Ranking Member
Anthony Fauci, NIH
Margaret Hamburg, FDA
Josh Sharfstein, FDA
Ali Khan, CDC

QUESTIONS SUBMITTED FOR THE RECORD
HEARING ENTITLED,
"ANTIBIOTIC RESISTANCE AND THE THREAT TO PUBLIC HEALTH"
SUBCOMMITTEE ON HEALTH
COMMITTEE ON ENERGY AND COMMERCE
UNITED STATES HOUSE OF REPRESENTATIVES
APRIL 28, 2010

Thomas Frieden, M.D., M.P.H.
Director
Centers for Disease Control and Prevention
U.S. Department of Health and Human Services

Representative Henry A. Waxman

Q1. You mentioned data from Europe demonstrating the link between animal antibiotic use and antibiotic-resistant microbes in people, in particular the example of avoparcin and vancomycin-resistant enterococcus. You also mentioned the data from Denmark, where antibiotics were banned for growth promotion uses for animals. Please evaluate the lessons from these European data and provide your views on any relevant lessons for the United States.

A. The Danish studies have focused on non-therapeutic use of antimicrobial agents in food-producing animals, particularly swine and broiler chickens. Non-therapeutic uses include promoting growth and improving feed efficiency; drugs for these purposes are typically given in feed.

- In 1995, the Danish government banned the non-therapeutic use of avoparcin for growth promotion in Denmark. In 1997, the commission of the European Union (EU) countries adopted the same ban for all of its member states.
- In 1998, Denmark banned use of virginiamycin for growth promotion. Also in 1998, the agriculture ministers in the EU voted to ban use of virginiamycin, bacitracin, tylosin, and spiramycin for growth promotion; this ban became effective for EU member states in 1999.
- The Danish cattle and broiler industries voluntarily stopped the non-therapeutic use of all antibiotics for growth promotion in February 1998.
- The Danish swine industry through voluntary and regulatory action stopped all non-therapeutic use of antibiotics for growth promotion in swine above 35 kg by February 1998 and for all age groups by December 1999.
- In 2002, the EU voted to phase out all non-therapeutic use of antibiotics for growth promotion (AGPs, i.e., all non-prescription use) beginning in 2006.

Effect of these actions[1,2,3,4,5,6]

[1] World Health Organization. 2003. Impacts of antimicrobial growth promoter termination in Denmark: The WHO international review panel's evaluation of the termination of the use of antimicrobial growth promoters in Denmark.Available at: http://www.who.int/salmsurv/en/Expertsreportgrowthpromoterdenmark.pdf.
[2] DANMAP. 2008. *Use of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from food animals, foods and humans in Denmark.* Available at: http://www.danmap.org/pdfFiles/Danmap_2008.pdf.

- While there has been an increase in therapeutic use of antimicrobials in animals, total antimicrobial consumption in animals in Denmark has decreased by over 50%. From 1998 to 2008, total antimicrobial consumption reduced from 100 to 49 milligrams of antimicrobials per kilogram of meat produced.
- Stopping the use of various non-therapeutic antibiotic growth promoters (e.g., avilamycin, avoparcin, spiramycin, tylosin, virginiamycin) has resulted in a major reduction in antimicrobial resistance as measured among several different bacterial species in food animals and food. This has been thoroughly documented in scientific publications from Denmark.
- Denmark measured total consumption of antimicrobial agents by food animals and resistance to those drugs among *Enterococcus* isolated from food animals and the foods derived from them.
- Resistance to these drugs among *Enterococcus* isolated from broilers, swine, and the meat from these animals decreased after AGPs were discontinued. However, in 2003, the World Health Organization (WHO) could not determine the ban's direct and total effect on antimicrobial resistance in humans because of limited data. Newer monitoring data available since then show that human resistance trends appear to be mirroring the decline in on-farm use of antibiotics; however, newer monitoring data on human resistance must be considered carefully. The trend must first be determined to be sustainable. Second, although the trend may mirror decreases in resistance in animals, more needs to be known about the potential causes for decrease in humans. If present, the trend toward decreased resistance is likely due to many factors including those aimed specifically at human antimicrobial usage and transmission of resistant bacteria.
- Weaner (swine) mortality increased several years before as well as a few years after non-therapeutic use stopped, but has drastically decreased in recent years, indicating that the termination had no effect on swine mortality.
- Production and economic impacts are described in a 2003 WHO report. The WHO reports that: "Overall, total volume of pork production in Denmark continued to increase in the period following the termination of antimicrobial growth promoters... The net costs associated with productivity losses incurred by removing antimicrobial growth promoters from pig and poultry production were estimated at 7.75 DKK (1.04 €) per pig produced

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[3] Aarestrup, F.M., A.M. Seyfarth, H.D. Emborg, K. Pedersen, R.S. Hendriksen, and F. Bager. July 2001. "Effect of Abolishment of the Use of Antimicrobial Agents for Growth Promotion on Occurrence of Antimicrobial Resistance in Fecal Enterococci from Food Animals in Denmark," *Antimicrobial Agents and Chemotherapy* 45(7): 2054-2059. Available at: http://aac.asm.org/cgi/reprint/45/7/2054.

[4] Boerlin, P., A. Wissing, F. M. Aarestrup, J. Frey, and J. Nicolet. 2001. "Antimicrobial Growth Promoter Ban and Resistance to Macrolides and Vancomycin in Enterococci from Pigs," *Journal of Clinical Microbiology* 39(11): 4193–4195. Available at: http://jcm.asm.org/cgi/reprint/39/11/4193.

[5] Evans, M.C. and H.C. Wegener. 2003. "Antimicrobial Growth Promoters and Salmonella spp., Campylobacter spp. In Poultry and Swine, Denmark," Emerging Infectious Diseases 9(4): 489-492. Available at: http://www.cdc.gov/ncidod/eid/vol9no4/pdfs/02-0325.pdf

[6] Gravea, K., V.F. Jensen, K. Odensvik, M. Wierup, and M. Bangen. 2006. "Usage of veterinary therapeutic antimicrobials in Denmark, Norway and Sweden following termination of antimicrobial growth promoter use," Preventive Veterinary Medicine 75(1-2): 123-132.

and no net cost for poultry. This translates into an increase in pig production costs of just over 1%."[7]

In general, subtherapeutic use has been shown to lead to an increase in resistant strains in animals. The European experience demonstrates that it is possible to stop these uses, reduce overall use of antibiotics in animals, reduce resistant circulating bacteria that can infect humans, and not have industry or consumers affected by decreased production or increased costs. Additional information, such as reliable data on quantities of antibiotics used in animals for various purposes and comprehensive on-farm studies of the relationship between use and resistance, would be needed to study the same effects in the United States.

Q2. The rates of foodborne illnesses—particularly those generated by antibiotic resistant organisms—have risen in this country. Ms. Capps asked about the National Antimicrobial Resistance Monitoring System data and suggested that much of the nation's meat and poultry products are tainted with some kind of antibiotic resistant bacteria. There are a number of studies, both in Europe and in the United States, suggesting a link between the use of certain antibiotics in animals and bacteria resistant to those antibiotics in food products and humans. For example, a study in Minnesota and Wisconsin found evidence indicating that antibiotic-resistant E. coli in people were likely to have came from poultry, while antibiotic-sensitive E. coli in people likely did not come from poultry (J.R. Johnson et al., *Antimicrobial Drug-Resistant Escherichia coli from Humans and Poultry Products, Minnesota and Wisconsin, 2002-2004*, Emerging Infectious Diseases (June 2007) (online at http://www.cdc.gov/EID/content/13/6/838.htm). Can you expand on this information, and comment on whether CDC believes such antibiotic resistant bacteria from animals and their meat have been transmitted to people?

A.

- CDC is familiar with the J.R.Johnson article referenced and concurs with the conclusions described in the study. Johnson et al analyzed the distribution and virulence genotypes of drug-susceptible and drug-resistant E. coli isolates from human volunteers and poultry products. They found that drug resistant E coli isolates from humans were more similar to drug resistant isolates from poultry then they were from drug susceptible isolates from humans. This work as well as other work from Johnson's group has contributed to the evidence that drug resistant E coli found in humans is most similar to that found in poultry.
- The National Antimicrobial Resistance Monitoring System (NARMS)[8] has demonstrated a steady and statistically significant increase in the prevalence of resistance to the two

[7] World Health Organization. 2003. Impacts of antimicrobial growth promoter termination in Denmark: The WHO international review panel's evaluation of the termination of the use of antimicrobial growth promoters in Denmark.Available at: http://www.who.int/salmsurv/en/Expertsreportgrowthpromoterdenmark.pdf.

[8] NARMS is a collaboration among CDC (human samples), FDA's Center for Veterinary Medicine (retail meats and animal feeds), and USDA's Food Safety and Inspection Service and Agricultural Research Services (animal samples). Participating health departments forward every twentieth non-Typhi Salmonella isolate, every Salmonella Typhi, every twentieth Shigella isolate, and every twentieth E. coli O157 isolate received at their public health laboratories to CDC for susceptibility testing. NARMS investigates outbreaks involving these bacteria and conducts research on resistance mechanisms.

most clinically important antimicrobial agents, ciprofloxacin and ceftriaxone, in *Salmonella* strains isolated from ill humans in the United States.

- A multidrug resistant (MDR) *Salmonella* Typhimurium emerged in the 1990s in cattle and in people, and has persisted since then (associated with ground beef).
- MDR *Salmonella* Newport emerged in 1998 in cattle and humans and has persisted since then (associated with ground beef).
- Resistance to ciprofloxacin in *Campylobacter* in poultry and people emerged in the late 1990s and steadily increased (associated with chicken and turkey).
- In 2005, FDA withdrew approval for fluoroquinolone use in poultry due to evidence it might be associated with resistant human infections.
- Although it has not been demonstrated conclusively in a single study that use of antimicrobial agents in food animals results in adverse human health consequences, numerous studies have demonstrated the movement of resistant pathogens through the food supply. Studies related to *Salmonella*, including many studies in the United States, have demonstrated that (1) use of antimicrobial agents in food animals results in antimicrobial resistance in food animals, (2) resistance strains are present in the food supply and commonly transmitted to humans, and (3) increases in resistant strains results in adverse human health consequences (e.g., increased hospitalization).[9],[10]

Q3. Mr. Dingell asked that you provide the level of your request for financial support for antimicrobial programs in the President's budget, the amount CDC has been given for these programs during each of the last 3 years, and the amount anticipated for the next 3 years. Please provide such information, including your professional judgment budget for the appropriate level of funding for antibiotic resistance programs at CDC.

A.

- In FY 2008, FY 2009, and FY 2010, antimicrobial resistance was funded ($16.9 million per year), either through specific Congressional appropriations or agency allocations.
- The FY 2011 President's Budget includes $8.7 million available to fund AR activities. The FY 2011 Budget also includes an increase of $19.6 million for the Emerging Infections program, which supports antimicrobial resistance activities, such as surveillance, technical assistance, and epidemiological and laboratory support.

CDC is committed to maintaining a strong AR program and is exploring the high value investments moving forward. CDC will work to prioritize funding through the Emerging infections program and antimicrobial resistance program to combat AR.

In CDC's professional judgment, to fully combat the growing problem of antimicrobial resistance, and to fully implement the CDC-coordinated sections of the Federal Inter-Agency Task Force on Antimicrobial Resistance *Action Plan* (surveillance, prevention and control), CDC requires an annual budget of $50 million phased in over a three year period (i.e. $30 million in FY 2012, $40 million in FY 2013, and $50 million in FY 2014). An incremental increase in the annual budget will allow for a stepwise expansion of surveillance, prevention and control

[9] Dutil et al., Emerg Infect Dis 2010

[10] Folster et al., Foodborne Pathog Dis 2010 and Zhao et al., Appl Environ Microbiol 2008.

activities described in the *Action Plan*. This does not include funding of antimicrobial resistance activities for specific diseases (such as tuberculosis and gonorrhea) funded through other CDC budget lines. This represents the professional judgment estimates of CDC staff on the size and scope of the AR activities, and is provided without regard to the competing priorities that the agency, the President, must consider to develop the Budget.

CDC would use this increase in funding to continue its antimicrobial resistance activities and add new applied research grants and demonstration projects; 75% of the division projects would be funded extramurally (both domestic and international) and 100% of the applied research grants and demonstration projects would be funded extramurally to domestic grantees. This increase in funding would also allow states via the Emerging Infections Program (EIP) and the Epidemiology and Laboratory Capacity (ELC) program to expand surveillance activities (e.g., to include antimicrobial resistance in healthcare-associated infections) and to increase state laboratory capacity to detect new and emerging resistance. CDC would also hire personnel to coordinate new surveillance activities and coordinate projects at state levels. This professional judgment budget also includes funding for capital expenses to reinforce select CDC reference laboratories and to develop and implement rapid diagnostic methods to determine the susceptibility of select microorganisms to new anti-infective agents. Funding would support an expansion of current databases of both antimicrobial use and antimicrobial resistance patterns, and expand web based reporting capabilities. Finally, the increase in funding would provide continued support for the Antimicrobial Resistance Task Force and allow CDC to plan and hold an antimicrobial resistance conference that will bring together scientists and consultants to update the Action Plan and discuss the latest scientific trends and developments in the field of antimicrobial resistance.

Professional Judgment Annual Budget for Antimicrobial Resistance Activities

Category	**Explanation**	**Cost (in millions)**		
		FY12	**FY13**	**FY14**
Continuing & new division projects	75% extramural, both domestic and international, Interagency Agreements	$7	$10	$12
Continuing & new research grants	100% extramural applied research grants and demonstration projects; educational activities	$5.5	$8.5	$15.5
Ongoing and new State-based AR activities	EIP and ELC funding to increase State-level capacity for surveillance, prevention activities, and reference laboratory services	$9	$10	$12
CDC Support for on-going and new AR	CDC funding for FTEs, laboratory supplies,	$8	$11	$10

activities	laboratory equipment, and software			
Task Force Support	Antimicrobial Resistance meeting, conference planning, Antimicrobial Resistance Task Force, consultants' meetings	$0.5	$0.5	$0.5
Total		$30	$40	$50

Q4. Your testimony before the Committee cited the theoretical risk of the use of antibiotics in animal feed. You also stated that you supported further action to ensure judicious use of antibiotics. Do you consider the use of antibiotics in animal feed for growth promotion or feed efficiency a judicious use of antibiotics, given these risks to public health?
A. CDC believes that the use of antimicrobials should be limited to protecting human and animal health. Purposes other than for the advancement of animal or human health should not be considered judicious use.

Q5. You spoke in yonr testimony about the need to judiciously prescribe antibiotics for humans. All antibiotics for humans in this country are prescribed under the oversight of a physician. In your view, should antibiotics used for animals be under the oversight of a veterinarian?
A. Yes, the use of medications for the prevention, treatment, and control of disease in animals should be under the supervision of a veterinarian. CDC supports the WHO's principles on containment of antimicrobial resistance in animals intended for food. Veterinarian oversight is a key principle in the "WHO Global Principles for Containment of Antimicrobial Resistance in Animals intended for Food" which is available at
http://whqlibdoc.who.int/hq/2000/WHO_CDS_CSR_APH_2000.4.pdf

Q6. I understand that the CDC's National Nosocomial Infections Surveillance (NNIS) does not track infections in long term care facilities or ambulatory surgical centers.
Can you explain why that is? In your view, would it be useful for the system to encompass long term care facilities and ambulatory surgical centers?
A. CDC agrees that it would be useful to expand healthcare-associated infection (HAI) surveillance and prevention activities to non-hospital settings. The National Healthcare Safety Network (NHSN – formerly NNIS) is successfully used by healthcare facilities in all 50 states (with 21 states using NHSN to fulfill their public reporting mandates) to collect and use HAI data for prevention activities, determine which practices help prevent HAIs, and to share data with other facilities within a healthcare system and/or public health agencies for collaborative prevention activities. Participation in NHSN has grown significantly in the past few years. As of March 20, 2009, over half of the approximately 5,000 U.S. hospitals are enrolled in and utilizing NHSN. Some states are already using NHSN for HAI surveillance and prevention activities in non-hospital settings. In October 2008, Colorado used American Recovery and Reinvestment Act funds awarded by CDC to extend its NHSN reporting of HAIs from ambulatory surgical centers. Additionally, there are 122 long-term acute care facilities, 51 outpatient surgical centers, and 109 hemodialysis facilities enrolled in NHSN.

Nationally, there are about 26,000 non-hospital facilities, including ambulatory surgical centers, dialysis centers, and long term care facilities where complex procedures are increasingly performed. CDC does currently have surveillance in these settings, though only a small portion of these non-hospital facilities are enrolled in NHSN because we are still refining the best way to capture surveillance data and modifying surveillance definitions for use in these settings. Currently, CDC's long-term care work group is using and modifying existing long-term care infection surveillance definitions in order to decrease surveillance burden on facilities. The FY 2011 Budget included an increase of $12.3 million for NHSN to support the expansion to 2,500 additional hospitals, and facilitate the implementation of prevention activities to achieve HHS HAI goals and targets.

Representative Jim Matheson

Q1. It is my understanding that in December 2007, the federal Interagency Task Force on Antimicrobial Resistance held a consultation in Atlanta bringing in 60 external consultants to help the task force revise the 2001 Action Plan on Antimicrobial Resistance. A draft revision was promised in 2008. We are now in 2010 and are waiting to see a product. a. Can you provide the committee with an update on the status of this action plan? Will this revised action plan contain benchmarks, as would be required by legislation that I introduced –the STAAR Act– to measure progress including for CDC, FDA and NIH? b. If no, then why not?

A. The *Action Plan* is currently under development and is expected to be released this year. This *Action Plan* includes benchmarks and timelines and will be made available for public comments upon release when it is published in the *Federal Register*. The *Action Plan* identifies four focused areas and each one has an agency coordinator and timeline:

- Surveillance: CDC is coordinating most action items
- Prevention and Control: CDC is coordinating most action items
- Research: NIH is coordinating most action items
- Product Development: FDA is coordinating most action items

CDC plans to regularly update the *Action Plan* with specific project and implementation steps at least every 2 years so that it becomes an even more informative and useful document.

Q2. In November of last year, President Obama, along with our European partners, announced the creation of a Transatlantic Task Force on Antibiotic Resistance to strengthen the antibiotic pipeline, develop interventions to address resistant infections in hospitals and communities, and opportunities to eliminate inappropriate uses in human and veterinary medicine. I am aware that it takes time to set up such an entity, but we are approaching 6 months from the announcement and I am not aware of word from the Administration on how this group is going to operate, what its charge will be, and whether it will include nongovernment experts. Including external experts to advise the government is a critical component of the Strategies to Address Antimicrobial Resistance (STAAR) Act, which I sponsored. a. What is the status of this international group and what is the charge of the transatlantic task force? b. Please provide the Committee with the list of participants, both domestic and international.

A. The Transatlantic Task Force on Antibiotic Resistance (Task Force) EU-US planning group has had a series of videoconferences and a kickoff meeting of the Task Force is scheduled for

June 2010. The Task Force will develop an action plan focused on the areas defined by the 2009 EU-US Summit declaration:

- Developing appropriate therapeutic use of antimicrobial drugs in the medical and veterinary communities
- Preventing both healthcare- and community-associated drug-resistant infections
- Developing strategies to improve the pipeline of new antimicrobial drugs

The Task Force is composed of experts and officials from the European Union and the United States. The United States is represented by the following individuals and agencies of the Department of Health and Human Services:
US Department of Health and Human Services (HHS), Office of the Secretary
Nils Daulaire, Director, Office of Global Health Affairs
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Centers for Disease Control and Prevention (CDC)
Denise Cardo, Director, Division of Healthcare Quality Promotion, National Center for Emerging and Zoonotic Infectious Diseases (proposed)
J. Todd Weber, CDC Liaison to the European Centre for Disease Prevention and Control, National Center for Immunization and Respiratory Diseases
Jean Patel, Deputy Director, Office of Antimicrobial Resistance

National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health
Dennis Dixon, Chief, Bacteriology and Mycology Branch, Division of Microbiology and Infectious Disease
Jane Knisely, Scientific Program Analyst, Bacteriology and Mycology Branch, Division of Microbiology and Infectious Disease

Food and Drug Administration
Edward Cox, Director, Office of Antimicrobial Products, CDER Drug Shortage Coordinator
Linda Tollefson, Director, FDA Europe Office

The European Union will be represented as follows:
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Andrzej Rye, Public Health Director, Directorate General Health and Consumers
Martinue Nagtzaam, Policy Officer, Directorate General Health and Consumers
Anna Lonnroth Sjoden, Deputy Head of Unit, Directorate General Research, Health-Infectious Diseases

European Centre for Disease Prevention and Control (ECDC)
Dominique Monnet, Senior Expert and Programme Coordinator, Scientific Advice Unit

European Medicines Agency (EMEA)
David Mackay, Head of Unit, Veterinary Medicines and Product Data Management

European Food Safety Authority (EFSA)
Marta Hugas, Scientific Coordinator, Head of Unit, Biological Hazard

Council of the European Union will be represented by the TRIO Presidency: Spain, Belgium, and Hungary
Jose Campos, Head of Unit, Antibiotic Laboratory, Instituto de Salud Carlos III
Nathalie Denecker, Clinical Assessor, Federal Agency for Medicines and Health Products
Karolina Borocz, Head of Department, National Centre for Epidemiology

Q3. In the STAAR Act, I have suggested a holistic approach to the problem of antibiotic resistance and establish a network of experts across the country to conduct regional monitoring of resistant organisms as they occur—which would be like a real time snapshot to pick up on problems early. Would you agree that there is importance in augmenting CDC's current surveillance system with some sort of expert surveillance network system?
A: CDC thinks it is important that legislative provisions enhance and complement CDC's existing surveillance systems, research and prevention efforts in order to avoid duplication of efforts. Surveillance is part of CDC's core mission and CDC agrees surveillance of resistant organisms is important. CDC's current surveillance system for antimicrobial resistance, the Emerging Infections Program (EIP), is a network of 10 state health departments working with collaborators in laboratories, healthcare facilities, and academic institutions to conduct population-based surveillance. Through this surveillance system, CDC provides national estimates of disease burden and tracks changes in disease burden over time for both resistant community-associated and healthcare-associated bacterial infections.

CDC also has other surveillance networks for bacterial resistance because surveillance strategies, goals and objectives vary for different problems: the National Healthcare Safety Network (NHSN) and the National Antimicrobial Resistance Monitoring System (NARMS). These surveillance systems complement EIP and are used to assess and monitor the scope, magnitude and trends of the antibiotic resistance problems and also to drive and direct prevention efforts, determine treatment recommendations, guide new drug development, and evaluate the effectiveness of prevention programs.

The National Healthcare Surveillance Network (NHSN) is a web-based surveillance tool for hospitals and state health departments to monitor healthcare-associated infection (HAI) rates, such as those caused by MRSA, *Clostridium difficile*, and multi-drug resistant gram-negative bacteria. Approximately half of U.S. hospitals (over 2,500) are currently enrolled in NHSN. The National Antimicrobial Resistance Monitoring System (NARMS) is a lab-based surveillance system between CDC, the Food and Drug Administration (FDA), the U.S. Department of Agriculture (USDA), and all 50 states. NARMS is used to detect resistance in enteric bacteria that are commonly transmitted from animals to humans through food, such as *Salmonella*, *Campylobacter*, and *E. coli* and monitors trends in the prevalence of resistance among bacteria isolated from humans, retail meats, and livestock.

CDC is taking steps to connect these systems including developing and launching networks of acute care facilities reporting HAI data through NHSN within the EIP, building an infrastructure to link pathogen-based evaluation, developing innovative surveillance methodologies, and translating surveillance data between population-based and hospital-based systems.

Q4. In your written testimony (p. 7) you reference that the VA reduced their rate of MRSA infections by 60% in part by implementing universal screening of all ICU and high-risk patients for MRSA (VA MRSA Initiative 2007). As part of the recommended test methods to identify patients colonized with resistant bacteria to prevent transmission, would CDC consider studying the effectiveness of rapid pre-surgical screening?
A. The subject of pre-surgical screening has been studied in the past and a recently published, well-conducted trial suggested that this may be an effective approach in select settings and for select surgical procedures (Bode LGM, Kluytmans JAJW, Wertheim HFL, et al. Preventing surgical site infections in nasal carriers of Staphylococcus aureus. *New England Journal of Medicine* 2010;362:9-17). CDC agrees that prevention research is needed to define the optimal strategy for using rapid pre-surgical screening, and we have much to offer in making sure such research is aligned with public health goals. CDC is currently providing technical assistance for a national survey of infectious disease physicians to assess the prevalence of pre-surgical *S. aureus* screening in the US.

CDC guidelines recommend that hospitals tailor their MRSA prevention strategies to their individual institution. CDC recommends that hospitals consider active surveillance as part of a comprehensive strategy to reduce MRSA infections if initial measures are not effective in reducing MRSA infections. CDC guidelines point out that the current science shows that active surveillance for MRSA might have an impact in reducing MRSA infections but only as part of a comprehensive strategy. What matters are the steps a hospital takes after it has identified colonized or infected patients and what subsequent prevention measure it uses. CDC guidelines recommend that hospitals achieve a reduction in MRSA using a comprehensive approach to prevention. For hospitals not showing a reduction using CDC's initial or first tier recommendations, CDC directs them to add additional measures, including screening of high risk patients for MRSA colonization, until success is demonstrated.

Q5. As you may know, The Infectious Diseases Society of America (IDSA) has urged the Administration and Congress to adopt the goal of developing 10 new antibiotics by 2020. Obviously, this is a large undertaking considering how few novel antibiotics there are currently in the pipeline. Has the Administration reviewed IDSA's 10 x '20 Initiative? What policies do you think this Committee should take into consideration to spur antibiotic development – especially for gram negative bacteria which has little, if anything in the pipeline?

[Please note that the response to this question was prepared by the National Institutes of Health, in response to the same question. We defer to NIH's expertise on this particular issue.]

The National Institute of Allergy and Infectious Diseases (NIAID), the lead component of the National Institutes of Health (NIH) for research on infectious diseases, is aware of the IDSA's initiative and supports its intent of bringing attention to the need for new antibiotic drug development. While there may be a number of policies that may provide incentives for the pharmaceutical and biotechnology industries to further engage in antibiotic drug development, the key to spurring antibiotic drug development is continued support of the drug development pipeline from the earliest stages through advanced development. NIAID recognizes the need to develop new antibiotic drugs and has a longstanding commitment to facilitate such development.

NIAID plays a critical role in the federal government's comprehensive efforts to combat the problem of antimicrobial resistance, with a particular emphasis on the issue of drug development. NIAID conducts and supports basic research to identify new antimicrobial targets and translational research to apply this information to the development of therapeutics; to advance the development of new and improved diagnostic tools for infections; and to create safe and effective vaccines to control infectious diseases and thereby limit the need for antimicrobial drugs. NIAID supports research and development of diverse products through a variety of mechanisms, including grants and contracts to academic laboratories, non-profit organizations, and small and large companies. Research and development of novel agents with activity against Gram-negative pathogens is being supported via all of these mechanisms.

Since 2002, NIAID has supported translational research efforts through its Challenge Grant/Partnerships Program, which was created to stimulate collaborative efforts and multidisciplinary approaches to rapidly advance promising candidate products for infectious diseases through the product development pathway. This program has uniquely fostered many new research collaborations between experts from different disciplines of academia and industry and has significantly accelerated the development of numerous new or improved countermeasures against many pathogens and toxins. Each year, the initiative targets different pathogens based on scientific needs and priorities, and selected Gram-negative pathogens have frequently been the focus of this program. Drug-resistant Gram-negative pathogens of concern were specifically targeted in the 2009 initiative.

To complement these collaborative research efforts, NIAID provides a broad array of pre-clinical and clinical research resources and services to researchers in academia and industry designed to facilitate the movement of a product from bench to bedside. By providing these critical services to the research community, NIAID can help to bridge gaps in the product development pipeline and lower the financial risks incurred by industry to develop novel antimicrobials. Importantly, development activities for several therapeutics with activity against Gram-negative bacteria are being carried out through these mechanisms.

Through an initiative initially introduced in 2007, NIAID has made a sustained effort to support clinical trials aimed at prolonging the effectiveness of currently available antibacterial drugs. The contracts awarded under this initiative support studies designed to help answer key questions about proper antimicrobial dose, treatment duration and whether antimicrobial treatment is necessary in all cases. The contracts provide for the design and conduct of Phase III and/or Phase IV clinical trials to test different therapeutic approaches and regimens that will reduce overexposure to antimicrobial drugs, thereby decreasing the likelihood of antimicrobial drug resistance and preserving the effectiveness of existing antimicrobials. For example, one of these clinical trials is focused on evaluating the optimal duration of therapy for urinary tract infections in children. Since urinary tract infections are caused primarily by Gram-negative organisms, the potential to decrease antibiotic use in this area would help to alleviate the selective pressure that drives the development of resistance in Gram-negative bacteria. This initiative will continue with new trials this year aimed at *pneumonia,* Gram-negative *bacteremia, acute otitis media and pulmonary tuberculosis.*

In late July, NIAID will co-sponsor, along with IDSA and FDA, a public workshop on antibiotic resistance. Topics for discussion will include an overview of the scale of the current bacterial resistance problem; the current understanding of the science and mechanisms of bacterial

resistance; the use of rapid diagnostics in diagnosis and management of bacterial infections; and the science of antibacterial drug development.

Representative Marsha Blackburn

Q1. On November 3rd of last year, President Obama, along with our European partners, announced the creation of a Transatlantic Task Force on Antibiotic Resistance [to streugthen the antibiotic pipeline, develop interventions to address resistant infections in hospitals and communities, and find opportunities to eliminate inappropriate uses in human and veterinary medicine]. Obviously, it takes time to set up such an entity, but now 6 months later, there has been no word from the Administration on how this group is going to operate, what its charge will be, and whether it will include non-government experts. Can you give us the status of this international group? Also, can you please provide the Committee with the list of participants, both domestic aud international?
A. The Transatlantic Task Force on Antibiotic Resistance (Task Force) EU-US planning group has had a series of videoconferences and a kickoff meeting of the Task Force is scheduled for June 2010. The Task Force will develop an action plan focused on the areas defined by the 2009 EU-US Summit declaration:

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Jose Campos, Head of Unit, Antibiotic Laboratory, Instituto de Salud Carlos III
Nathalie Denecker, Clinical Assessor, Federal Agency for Medicines and Health Products
Karolina Borocz, Head of Department, National Centre for Epidemiology

Q2. In its Fiscal Year 2011 Congressional Justification, CDC calls antimicrobial resistance "one of the world's most pressing public health problems." However, within the Preparedness, Detection, and Control of Infectious Diseases program's proposed budget, CDC's already severely strapped Antimicrobial Resistance budget would be cut dramatically by $8.6 million—just over 50 percent! The FY2011 budget would allow only 20 state/local health departments and health care systems to be funded for surveillance, prevention, and control of antimicrobial resistance, down from 48 this past year. Can you tell us which states will no longer receive funding under the Antimicrobial Resistance program at CDC?
A. The FY2011 budget request would allow 20 state/local health departments and health care systems to be funded for surveillance, prevention, and control of antimicrobial resistance. It is not possible at this time to determine which states would receive funding. Its possible that more state and local health departments could be funded through the $ 19 .6 million increase in the emerging infections program.

Q3. Additionally, in the budget justification, CDC states that the number of states to receive funds under the Get Smart in the Community program will go from 12 to zero. Can you give us the rationale for your decision to cut back so drastically on this important program given the dire health implications of antimicrobial resistance?
A.. The program has contributed to a 25 percent reduction in antimicrobial use per outpatient visit for presumed viral infections. In addition, more than 959 campaign partners and 166 funded state-based programs collaborate with the Get Smart campaign.Given competing priorities, CDC is looking for ways to efficiently use funding and make difficult decisions based

on available funds. Activities will continue on a prioritized basis, as funding exists through the Emerging Infections program.

Q4. For the past 18 months or more, there has been no full-time director for the Antimicrobial Resistance program, since the departure of the most recent permanent director. What is the status of appointing a new director to oversee the Antimicrobial Resistance programs at CDC?

A. CDC's Director of the Office of Antimicrobial Resistance (OAR) retired in April 2010. An acting director has been appointed and will remain in place until CDC hires a new permanent director. CDC is conducting a national search for an individual who is a recognized leader in the field of infectious diseases and antimicrobial resistance.

STATEMENT FOR THE RECORD
Subcommittee on Health, Committee on Energy & Commerce
United States House of Representatives

For the Hearing On Antibiotic Resistance And The Use Of Antibiotics In Animal Agriculture

July 14, 2010

RE: H.R. 1549/S. 619, The Preservation of Medical Treatment Act

The San Francisco Medical Society is in full support for H.R. 1549, the "Preservation of Antibiotics for Medical Treatment Act" (PAMTA- H.R. 1549/S. 619).

As a 140-year old organization of over 1,000 physicians in practice and research, we have been following and advocating for more rational and healthy practice and policy on this topic for a decade. The California Medical Association and American Medical Association both adopted our policy resolution urging curtailment of the non-therapeutic use of antibiotics in agriculture, and scientific research conducted since that time has made it increasingly clear that the policies embodied by PAMTA are urgently needed.

Medical experts across the globe increasingly agree that the growth of drug resistant bacterial infections is a looming public health crisis and acknowledge that the wide scale use of antibiotics in food animal production is a significant contributor to the problem.

By reducing the use of antibiotics where they are being applied most inappropriately and in the greatest numbers, PAMTA would represent a crucial step forward in the fight against antimicrobial resistance. We urge Congress to swiftly pass this legislation to ensure the health of our citizens.

Sincerely,

Michael Rokeach, MD
President

Steve Heilig, MPH
Director

San Francisco Medical Society
1003A O'Reilly Avenue
San Francisco, CA 94129
(415)561-0850x270
http://www.sfms.org

Physicians for Social Responsibility-Los Angeles

The physician and health advocate voice for a world free from nuclear threats and a safe, healthy environment for all communities.

PSR-LA

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In memoriam

Shirley Magidson, Emerita
In memoriam

Congressman Henry Waxman
2204 Rayburn House Office Building
Washington, D.C. 20515
Telephone (202) 225-3976 Fax (202) 225-4099

On behalf of the over 4,000 physicians and health professionals of the Physicians for Social Responsibility-Los Angeles (PSR-LA), I am writing to express support for H.R. 1549, the "Preservation of Antibiotics for Medical Treatment Act" (PAMTA- H.R. 1549/S. 619). Antibiotics are one of the most useful and important medical advances in recent history. Their effectiveness, however, is being compromised by bacterial resistance, arising in part from excessive use of antibiotics in animal agriculture.

Up to 70 percent of all antibiotics sold in the U.S. are used on industrial farms in healthy food animals, according to The Union of Concerned Scientists. This makes the United States one of the biggest users of antibiotics in food animal production on a pound per pound basis. Many of the antibiotics used in food animal production are identical or from the same family as drugs used in human medicine to cure serious disease. While bacteria are killed through the proper use of antibiotics, improper use on the farm allows bacteria to become resistant. Resistant germs are left to grow and multiply, promoting the development of antibiotic-resistant bacteria that can spread to humans. Resistant bacterial infections are harder to treat, require longer hospital stays and possibly other interventions, generate $16.6 billion to $26 billion per year in extra costs to the United States health care system, and lead to over 90,000 deaths per year nationwide.

Congress has before it a common sense solution that would address the growing human health threat posed by antibiotic resistance. If passed into law, PAMTA would withdraw seven classes of antibiotics vitally important to human health from routine use in food animal production unless animals or herds are sick with disease or unless drug companies can prove that their use does not harm human health.

PAMTA is supported by our national organization, Physicians for Social Responsibility (PSR), and by leading medical organizations including the American Medical Association, the American Public Health Association, the Infectious Diseases Society of America, the World Health Organization, and the American Academy of Pediatrics. The Food and Drug Administration recently recommended that the use of medically important human antibiotics in food animal production "should be limited to those uses that are considered necessary for assuring animal health." While this is step in the right direction, it is clear that legislative action will be necessary if this urgent public health threat is to be addressed.

PAMTA would represent a crucial step forward in the fight against antimicrobial resistance by reducing the use of antibiotics where they being applied most inappropriately and in the greatest numbers. On behalf of PSR-LA, I urge Congress to swiftly pass this legislation to ensure the health of our citizens.

Sincerely,

Martha Dina Arguello

Martha Dina Arguello
Executive Director,
Physicians for Social Responsibility-Los Angeles

Health Care Without Harm
the campaign for environmentally responsible health care

CAMPAIGN HEADQUARTERS

12355 SUNRISE VALLEY DRIVE
SUITE 680
RESTON, VA 20191
T: 703.860.9790
F: 703.860.9795
EMAIL: INFO@HCWH.ORG
WWW.NOHARM.ORG

The Honorable Henry A. Waxman
Chairman
Committee on Energy and Commerce
U.S. House of Representatives
2125 Rayburn House Office Building
Washington, DC 20515

July 12, 2010

Dear Representative Waxman:

Health Care Without Harm is pleased to submit the attached documents for the Record on the hearing "Antibiotic Resistance and the Use of Antibiotics in Animal Agriculture" of the House Committee on Energy and Commerce Health Subcommittee, July 13, 2010. We will submit through Representative Schakowsky.

Since the introduction of the "Preservation of Antibiotics for Medical Treatment Act," HCWH has gathered information from the health care sector in support of the legislation. We are submitting more than 1000 names of physicians and other health care practitioners who have written to support legislation that would reduce or prohibit the non-therapeutic use of antibiotics in food animals. We are also submitting a list of more than 70 hospitals that have indicated their support for such legislation by signing a petition.

In addition, more than 300 hospitals have signed the Health Care Without Harm Healthy Food in Health Care Pledge, which, among other commitments, seeks to purchase foods produced without the use of non-therapeutic antibiotics for the hospital food service, for patients and staff.

We believe that legislation is necessary to preserve the effectiveness of our existing antibiotics. Antibiotic resistant bacterial infections are a serious concern for individuals, communities and our health care delivery system. Patients suffer longer illnesses and pay higher medical costs, and health practitioners are left with little means to protect their patients or themselves from bacterial infection. The Centers for Disease Control and Prevention estimates that 60,000 Americans die annually from resistant infections. The American College of Physicians estimates that $30 billion is spent on the cumulative effects of antimicrobial resistance each year (including multiple drug regimens, extra hospital days, additional medical care and lost productivity).

Despite the rising rates and immense medical costs of antibiotic resistance, antibiotics and related drugs are routinely added to the feed of livestock and poultry not to treat diagnosed disease, but to promote faster growth and compensate for unsanitary living conditions. In 2003, the U.S. Institute of Medicine/ National Academy of Science stated that "substantial efforts must be made to decrease inappropriate

overuse [of antibiotics] in animals and agriculture" and that decreasing "antimicrobial use in human medicine alone will have little effect on the current [antibiotic-resistant] situation."

Health Care Without Harm is an international coalition of more than 430 organizations in 52 countries, working to transform the health care industry worldwide, without compromising patient safety or care, so that it is ecologically sustainable and no longer a source of harm to public health and the environment. For more information on HCWH, see www.noharm.org.

Thank you for the opportunity to submit these documents for the record.

Sincerely,

Jamie Harvie
Chair, Healthy Food Initiative
HCWH

Cc: The Honorable Janice D. Schakowsky



the campaign for environmentally responsible health care

WWW.NOHARM.ORG

July 12, 2010

Dear Senator or Representative:

On behalf of Health Care Without Harm and the undersigned hospitals and health systems, we **urge you to support the Preservation of Antibiotics for Medical Treatment Act (S. 619/H.R. 1549)**. This legislation is necessary to keep our precious antibiotics working for people when they are faced with potentially life-threatening illnesses. In addition to the hospitals and health systems listed below. PAMTA is supported by a growing number of medical and public health organizations including the American Medical Association, American Nurses Association, American Public Health Association, and the American Academy of Pediatrics.

Antibiotics were one of the greatest medical innovations of the last century. But today, physicians are seeing more and more patients with more expensive, more threatening infections that are resistant to multiple antibiotics. The Centers for Disease control estimates that 60,000 Americans die annually from resistant infections. The American College of Physicians estimates that $30 billion is spent on the cumulative effects of antimicrobial resistance each year (including multiple drug regimens, extra hospital days, additional medical care and lost productivity).

The Institute of Medicine/National Academy of Science has stated that, "Clearly, a decrease in antimicrobial use in human medicine alone will have little effect on the current [antibiotic-resistant] situation. Substantial efforts must be made to decrease inappropriate overuse in animals and agriculture as well." Nevertheless, medically important antibiotics and related drugs continue to be routinely added to the feed of livestock and poultry that are not sick, to promote faster growth and compensate for unsanitary living conditions. This unnecessary overuse of antibiotics promotes the development of resistance and as well, undercuts their effectiveness for treatment of sick animals.

The Preservation of Antibiotics for Medical Treatment Act will protect public health by requiring automatic phase out of the use of seven classes of antibiotics designated as "critically important" or "highly important" in human medicine as agricultural feed additives unless FDA concludes within two years that their use does not contribute to antibiotic resistance affecting humans. Passage of this bill would be an important step in addressing the very real threat of antibiotic resistance and preserving the effectiveness of existing antibiotics for treatment of both human and animal diseases.

We urge you to support the Preservation of Antibiotics for Medical Treatment Act and undertake all measures necessary to ensure its ultimate enactment.

Sincerely,

Health Care Without Harm

Fletcher Allen Health Care, VT

Porter Medical Center, VT

Fairview Hospital, MA

Covenant Health Systems, New England (14 facilities)

Regis Care Center, NY

Swedish Covenant, IL

St. Luke's, MN

Sacred Heart Hospital, WI

Mercy Medical Center, Baltimore , MD

Oregon Health and Science University, OR

Catholic Healthcare West, AZ , NV, CA (40 facilities)

St. Joseph Health System - Sonoma County, CA (7 facilities)

Health Care Without Harm

the campaign for environmentally responsible health care

CAMPAIGN HEADQUARTERS

12355 SUNRISE VALLEY DRIVE
SUITE 680
RESTON, VA 20191
T: 703.860.9790
F: 703.860.9795
EMAIL: INFO@HCWH.ORG
WWW.NOHARM.ORG

Dear Senator or Representative:

We, the undersigned nurses, doctors, dietitians and other health practitioners are writing to urge you to support the Preservation of Antibiotics for Medical Treatment Act (S. 619/H.R. 1549). We believe that this legislation is necessary to preserve the effectiveness of our existing antibiotics.

Antibiotic resistant bacterial infections are a serious concern for individuals, communities and our health care delivery system. Patients suffer longer illnesses and pay higher medical costs, and health practitioners are left with little means to protect their patients or themselves from bacterial infection. The Centers for Disease Control and Prevention estimates that 60,000 Americans die annually from resistant infections. The American College of Physicians estimates that $30 billion is spent on the cumulative effects of antimicrobial resistance each year (including multiple drug regimens, extra hospital days, additional medical care and lost productivity).

Despite the rising rates and immense medical costs of antibiotic resistance, antibiotics and related drugs are routinely added to the feed of livestock and poultry not to treat diagnosed disease, but to promote faster growth and compensate for unsanitary living conditions. In 2003, the U.S. Institute of Medicine/ National Academy of Science stated that "substantial efforts must be made to decrease inappropriate overuse [of antibiotics] in animals and agriculture" and that decreasing "antimicrobial use in human medicine alone will have little effect on the current [antibiotic-resistant] situation." Delaying action only exacerbates the problem.

As individuals, we join with the American Medical Association, the American Academy of Pediatrics, the American Nurses Association and many other public health organizations. Please support the Preservation of Antibiotics for Medical Treatment Act and undertake all measures necessary to ensure its ultimate enactment.

Sincerely,

ALABAMA

Paula Gasser, RN; Birmingham, AL
Elisa Mejia, RN BSN/BA Infection Preventionist; Birmingham, AL
Mary Pate, RN, DSN; Birmingham, AL
Mariann Schmitz, MPH, CIC; Birmingham, AL
Arlene Morris, RN, MSN, EdD, CNE; Montgomery, AL
charlene roberson, RN; montgomery, AL
Thomas Hodges, CHMM; Opelika, AL
Helen Wilson, RN, MSN; Wetumpka, AL

ARIZONA

Diane Gold, RN, MSN, CSN; Clarkdale, AZ
Gary Spivey, MD; Douglas, AZ
Sara Gibson, MD; Flagstaff, AZ
April Laliberte, ; Flagstaff, AZ
Chandy Leverance, ; Globe, AZ
Donna Farney, RD, MS; Goodyear, AZ
Michelle Dorsey, MD; Mesa, AZ
Carl Nichols, CDM CFPP; Peoria, AZ
Julie Spelman, RD MBA; peoria, AZ
Caleb Laieski, ; Phoenix, AZ
Karen Peterson, ; Phoenix, AZ
Christopher Jentoft, MD; Scottsdale, AZ
Carolyn Maxon, ; Scottsdale, AZ
Bonnie Roill, RD, MA; Scottsdale, AZ
marlene bluestein, md; tucson, AZ
Klara Dannar, RN; Tucson, AZ
Raymond Graap, M.D.; Tucson, AZ
Schuyler Hilts, MD, FACP, FACNP; Tucson, AZ
Janet Hughes, RN; Tucson, AZ
Sharon McDonough-Means, MD; Tucson, AZ
Fayana Richards, ; Tucson, AZ
Eve Shapiro, MD; tucson, AZ
Linda Taylor, ; Tucson, AZ
Barbara Warren, MD, MPH; Tucson, AZ

CALIFORNIA

Joyce Lashof, MD,FACPM; Alameda, CA
george chang, DO; arcadia, CA
ena valikov, dvm; bellflower, CA
Joel Kreisberg, DC; Berekely, CA
David Dresser, ; Berkeley, CA
Todd Jailer, ; Berkeley, CA
Hercules Morphopoulos, DDS; Berkeley, CA
Sanghyuk Shin, MSc; Carlsbad, CA
Bruce Burdick, MD; Carmichael, CA
Lucinda Crawford, ; Chino Hills, CA
Carla Jackson, MPH; Claremont, CA
Virginia & William Corzine, ; Cloverdale, CA
alison negrin, ; concord, CA
Robert Grisnak, RN; Daly City, CA
Terrie Kurrasch, MPH, FACHE; Emeryville, CA
Karen Arnold, RD; Fairfax, CA
Angel Lee, ; Fremont, CA
Mike Starry, MLS; Fresno, CA
Arthur Smith, PhD; Garden Grove, CA
Sanford Newmark, md; Half Moon Bay, CA
Tesds Lusher, MD; Healdsburg, CA
Lorraine Moriarity, RN; Hemet, CA
Robert Rosenberg, DDS, DScD; Kentfield, CA
Pedro Sun, ; la mesa, CA
Pejman Katiraei, DO; Loma Linda, CA
Amy Blomquist, ; Loma Mar, CA
Robert Frcek, CPA; Los Angeles, CA
Dawn Lee, ; Los Angeles, CA
Lenard Lesser, MD; Los Angeles, CA
Bruce Hyman, MD; los gatos, CA
Steven Freedman, MD; Martinez, CA
Oscar Firschein, ; Menlo Park, CA
David Chittenden, ; Mill Valley, CA
stephen pardys, MD; mill valley, CA
JESSIE MULLEN, NONE; MONTEREY, CA
Kathi Randall, RN, MSN, Neonatal CNS &NP- BC; moreno valley, CA
Jerry Abajian, MD; Napa, CA
Kathleen Young, ; Northridge, CA
SCOTT AMUNDSON, ; OAKLAND, CA
Emily Cronbach, MD; Oakland, CA
Arthur D'Harlingue, MD; Oakland, CA
J. Huston, CEC, CDM, CFPP; Oakland, CA
Jennifer Jackson, M.A.; Oakland, CA
Jeffrey Johns, MD; Oakland, CA
Eleanor Luce, MD; Oakland, CA
Laurence Platt, MD, MPH; Oakland, CA
Charles Rath, MD; Oakland, CA
Kimi Schell, ; Oakland, CA
Kathryn Williams, MD; Orinda, CA
David Campen, MD; Palo Alto, CA
Ivan Gendzel, MD; Palo Alto, CA
John Mark, MD; Palo Alto, CA
Daniel Asimus MD, MD; Pasadena, CA
Mary Henriques, MPH; Pasadena, CA
John Tsai, MD; Pomona, CA
marianne gerson, MD; portola valley, CA
Jack Kabak, MD; Portola Valley, CA
Judith Murphy, MD; Portola Valley, CA
Anthony DeRiggi, MD; Sacramento, CA
Alan Moritz, MD; Sacramento, CA
Harry Wang, MD; Sacramento, CA
Lee Lipsenthal, MD; San Anselmo, CA
Jerri Smith, RDCS; San Bernardino, CA
Thomas Newman, MD, MPH; San Carlos, CA

Anthony Earthen, ; San Diego, CA
Caroline Frederick, MBA, MS; San Diego, CA
Karmyn Garcia, LEED AP; San Diego, CA
Michael Mae, ; San Diego, CA
Dana Riccio, RD; San Diego, CA
cathy wise, ; san fran, CA
Erin Amerson, MD; San Francisco, CA
Helen Chang, MD; San Francisco, CA
Karen Duderstadt, PhD, RN, CPNP; San Francisco, CA
Robert Gould, MD; San Francisco, CA
Lisa Hartmayer, BS, RN; San Francisco, CA
Sarah Janssen, MD, PhD, MPH; San Francisco, CA
Cathlin Milligan, MD; San Francisco, CA
Zeljko Milovanovic, MD; San Francisco, CA
judith ostapik, ; san francisco, CA
Kelly Pfeifer, MD; San Francisco, CA
Joan Saxton, M.D.; San Francisco, CA
Joseph Spaulding, MD; San Francisco, CA
George P. Susens, MD, MD; San Francisco, CA
Susan Vickers, ; San Mateo, CA
Lee FitzGerald, Registered Nurse; San Rafael, CA
Douglas Gerstein, MD; San Rafael, CA
joseph gutstadt, MD-Ret.; san rafael, CA
Susan Clarke, RN; Santa Barbara, CA
John La Puma, MD; Santa Barbara, CA
Janet Lengsfelder, RN; Santa Barbara, CA
Patricia Rupel, RN; Santa Clara, CA
Deane Bussiere, ; santa cruz, CA
lisa segnitz, md; Santa Cruz, CA
Stephanie Singer, RD; Santa Cruz, CA
Sister Janet Corcoran, ; Santa Maria, CA
Linda Hansen, CDM; Santa Rosa, CA
Marsha Nunley MD, MD; Sausalito, CA
Laura Dick, PhD, RD; South Lake Tahoe, CA
Trisha Reece, ; Studio City, CA
Gerri French, RD; Summerland, CA
Evelyn C Lundstrom, ; Sunnyvale,, CA
Alicia Bright, CNS, RN; Tiburon, CA
Andy Coren, MD; Ukiah, CA
Andrea McCullough, MD; Ukiah, CA
Marilyn Klakovich, RN; Upland, CA
Susan Zabo, ; Valencia, CA
Ronald Bieselin, MD; Vallejo, CA
Sandra Rigney, ; Walnut Creek, CA
Martin Bronk, ; Woodside, CA

COLORADO

JEANNE REISIG, MA; Aurora, CO
Michael Vasil, Ph.D.; Aurora, CO
Sarit Schneider, CNM; Boulder, CO
Richard Steinberg, MD; Boulder, CO
David Howard, ; colorado springs, CO
Carolyn Coker Ross, MD, MPH, MD, MPH; Denver, CO
Roberta M Richardson, MD; Evergreen, CO
Lisa Henbest, RN; Highlands Ranch, CO
Kristi Ennis, ; Lafayette, CO
Francis Babineau, PE; Littleton, CO
MICHELLE HOSACK, RD; Rifle, CO

CONNECTICUT

Constance Byam, RN; Andover, CT
Bethany Hricu, RD; Avon, CT
Evelyn Angry-Smith, ; Bloomfield, CT
Ana Chambers, ; Canton, CT
Sharon Riccardi, ; East Hartford, CT
lorraine barker, ; goshen, CT
Mary Cobb, RN; Guilford, CT
Susan Pinkham, RD; Hartford, CT
Natalia Piendel, ; Manchester, CT
william whitehead, ; new canaan, CT
Mary Cranley, RN/NP; Oakland, CT
Nick DeDominicis, ; Old Saybrook, CT
Lisa Burch, LCSW; South Windsor, CT
Maureen Clinton, NCCMHC; Tolland, CT
kathleen McLaughlin, ; Tolland, CT
Gabrielle Riola, RD; Tolland, CT
Anne Gallagher, ; washington depot, CT
Shellie Jones, ; Willimantic, CT
Heidi Krajewski, ; Windsor Locks, CT
kathy murphy, RN/MSN; Wolcott, CT

DISTRICT OF COLUMBIA

Matt Aleshire, ; Washington, DC
Helen Hagerty, ; Washington, DC
Elizabeth Ide, MA; Washington, DC
Tamar Klaiman, ; Washington, DC
Marjorie McKnight, MD; Washington, DC
Shannon Pryor, MD; Washington, DC

DELAWARE

Ann Darwicki, RN; Bear, DE
Sarah Bucic, MSN, APRN-BC; Delaware City, DE
Kelly Rossi, MS, RD; Frankford, DE
Tish Gallagher, RN, PhD, CNE; New Castle, DE
Joyce Linus, NCSN, RN; New Castle, DE
Michelle Lauer, RN, MSN, BC; Wilmington, DE
christine madden, Ph.D. (ABD); Wilmington, DE
Catherine Maguire, RN, MSN; wilmington, DE
Sheila Sharbaugh, RN; Wilmington, DE

FLORIDA

Adam LIPKIN, MD; ENGLEWOOD, FL
Noelle Lipkin, ARNP; Englewood, FL
Carol OBrien, RN MA CNAA; Fort Lauderdale, FL
susan Milette, RN; Ft. Pierce, FL

Betty Finnk, RN, CIC; Hollywood, FL
Brittany Marshall, ; Lake Mary, FL
susan luck, R N; Miami, FL
HILDA WONG, ; MIAMI, FL
Thomas Perez, R.Ph.; Mims, FL
linda mililllo wilson, rn,cic; pbg, FL
Karen Boothe, RN; pembroke pines, FL
connie sherl, RN; Pembroke Pines, FL
Molly Dodge, MD; St.Petersburg, FL

GEORGIA

Emily Moore, MS, RD, LD; Albany, GA
Hannah Jacskon, ; Athens, GA
Tiffany Barrett, ; Atlanta, GA
Erin Bradley, ; Atlanta, GA
Jessica Enders, RD/LD; Atlanta, GA
jessica johnson, MS, RD, LD; atlanta, GA
Francoise Maillet, RD, LD; Atlanta, GA
Liz McGovern, ; Atlanta, GA
Lynne Ometer, RD; Atlanta, GA
Jessica Principe, MS, RD, LD; Atlanta, GA
Kip Slaughter, RD, LD; Atlanta, GA
Patti Willard, citizen; Atlanta, GA
Lisa Byrns, RN; Brunswick, GA
Elizabeth Gilchrist, ; Decatur, GA

GUAM

Leonora Urbano, RN; Hagatna, GU

HAWAII

Kawika Liu, MD, PhD, JD; Honolulu, HI

IOWA

Cathy Chenard, RD; Coralville, IA
patricia fuller, RN; Council Bluffs, IA
Angie Tagtow, MS, RD, LD; Elkhart, IA
Kristin Breitbach, BSN; Iowa City, IA
Julia Buchkina, MD; Iowa City, IA
Veronika Kolder, MD, MD; Iowa City, IA
christine ziebold, MD PhD MPH; Iowa City, IA
Colleen Clopton, ; Jefferson, IA
Diane Foster, ; Jefferson, IA
Hayley Hegland, ; North Liberty, IA
Maureen McCue, MD PhD; Oxford, IA
John Rachow, PhD, MD; Oxford, IA

IDAHO

Robin E Pattillo, PhD, RN, CNL; Blackfoot, ID

ILLINOIS

Debra Bergander, ; Chicago, IL
Martha Bergren, RN; Chicago, IL
henry buehler, ; chicago, IL
Jose Cuevas, Advocate; Chicago, IL
Danielle Dupuy, MPH; Chicago, IL
Donna Nelson, MS, RD; Chicago, IL
Danielle Thomas, MD candidate, class of 2013; Chicago, IL
Matthew Turner, ; Chicago, IL
Steven Verzi, ; Chicago, IL
Judith Gibbs, b.s.n.; Decatur, IL
Cindy Ferguson, CHMM; downers grove, IL
Rachel Greeley, LCSW; Evanston, IL
Alvin Paden, Retired; Evanston, IL
Lynnette Jones, RD; Glen Ellyn, IL
Kay Butler, CDM, CFPP; Highland, IL
Maureen Anger, RN; LAke forest, IL
Amy Switzer, RN, MS, CPHQ; Paris, IL
Rebecca Crane, RN, MSN, CIC; Quincy, IL
elizabeth holland, MD; river forest, IL
Laura Wenger, RN; Schaumburg, IL
Sue Schleyhahn, RN; Springfield, IL
Mary Johnson, RN; Wheaton, IL
Maria Schnaper, RN; Wilmette, IL
Marta Keane, ; Yorkville, IL

INDIANA

Stephen Ashkin, ; Bloomington, IN
Christine Carver, RD, CD; Bloomington, IN
Joyce , ; Bloomington, IN
SHARON RICKETTS WILLIAMS, Recycling Coor; Covington, IN
Anne E Belcher, ; Indianapolis, IN
Alan Berry, ; Indianapolis, IN
Mary Lou Hulseman, MD; Indianapolis, IN
Eugene Justus, DO; Indianapolis, IN
Maria Madar, BS Health Education; Indianapolis, IN
Charles Platz, MD; Indianapolis, IN
Heather Woods, RRT; Indianapolis, IN
arlene shannon, ; LaGrange, IN
CHERYL CORBIN, RN; LINTON, IN
Joseph Vasta, ; South Bend, IN
Fredric Salstrom, ; St. Mary of the Woods, IN
Rhonda Blevins, MT(ASCP), Infection Preventionist; Waterloo, IN

KANSAS

AMI RUGHANI, Medical Student; Kansas City, KS
Nicole Tichenor, ; Lawrence, KS
Jill Pettis, ; Merriam, KS
Jasmine Thompson, ; Wichita, KS

KENTUCKY

Wanda VanLandingham, ; Falmouth, KY
James Roach, MD; Midway, KY

LOUISIANA

Alex Choi, ; New Orleans, LA
Wendy Hounsel, ; New Orleans, LA
Ann Hsieh, MD Candidate 2013; New Orleans, LA
krisztian magyar, ; new orleans, LA

Peggy Verret, RN, MA, BC-NH; Slidell, LA

MASSACHUSETTS

Marianne Pappaceno, RD, LDN; Abington, MA
Jennifer Taylor, ASCP; Acton, MA
Jennifer Stinson, RD, LDN; Amesbury, MA
samuel gladstone, md; amherst, MA
Pamela Sierra, OTR; Andover, MA
Cynthia Sauer, RN; Attleboro, MA
Deborah Boudrow, RD LDN; boston, MA
Kerri Hawkins, MS, RD, LDN; Boston, MA
Lynn Larsen, RD, LDN; Boston, MA
Sean Palfrey, MD; Boston, MA
julie rollins, MA; boston, MA
Nicholas Sambuco, ; Boston, MA
Kate Speach, ; Boston, MA
Julie Thayer, MPH; Boston, MA
Katherine Villers, M.A.; Boston, MA
James Warth,M.D., M.D.; Boston, MA
Lisa Ferreira, MS, RD, LDN; Brighton, MA
Vanessa Kane, RD, LDN; Brighton, MA
Emily McPhee, RD, LDN; Brighton, MA
Margaret Scholl, ; Brockton, MA
Colleen Caldwell, B.A; Brookline, MA
Perrine Marcenac, ; Brookline, MA
Lauren Oliver, Ms, RD, LDN; Brookline, MA
Janel Ovrut, RD, LDN; Brookline, MA
Tara Nelson, MS, RD, LDN; cambridge, MA
Sara Valverde, ; Cambridge, MA
Josefine Wendel, MS, RD, LDN; Cambridge, MA
Aaron Manders, RD; Cambridge MA, MA
Kristen Pufahl, MS, RD, LDN; Charlestown, MA
Deborah Woods, ; Cheshire, MA
mark richards, MSW, LICSW; chester, MA
Jonathan Ginzberg, Lic.Ac.; Cummington, MA
Lisa Harvey, MD; Cummington, MA
Elizabeth Quinn, ; Dracut, MA
Stephanie Freitas, ; East Freetown, MA
SHARON SOUZA, RN; FAIRHAVEN, MA
Melissa Cabral, ; Fall River, MA
regina brady, ; feeding hills, MA
Louise Bendel, MS, RD, LDN; Framingham, MA
alice Ng, RD; Framingham, MA
Colleen Brannelly, RN; Franklin, MA
Peter Antalek, CTS; Grafton, MA
Stephanie Chalupka, EdD, RN, PHNCNS-BC, FAAOHN; Grafton, MA
Jane Griffin, RDMEd,CDE; hingham, MA
Barbara Casaceli, RD, LDN; Hudson, MA
Bridget Lee, MD; Jamaica Plain, MA
Bronwyn Williams, ; Jamaica Plain, MA
Lydia Bonilla, LPN; Lawrence, MA
Tony Leroka, LPN; Lawrence, MA
David Ndungu, RN; Lawrence, MA
Siobhan McNally, MD, MPH; Lenox, MA
Bill Ravanesi, MA,MPH; Longmeadow, MA
Sharon Berkley, LPN; Lowell, MA
Misty Mahoney, LPN; Lowell, MA
Linda Sullivan, RD, LDN; Lynn, MA
Alisa Himelfarb, RD; Marlborough, MA
Jessica Prohn, RD, LDN; Marlborough, MA
Christine Rymsha, MS, RD, LDN.; Marlborough, MA
Claudia Mills, RN; Mattapoisett, MA
Jacquie Higgins, RD; Newburyport, MA
Maria Morales, CNA; North Andover, MA
Martha Nathan, MD; Northampton, MA
Robert Rechtschaffen, MD; northampton, MA
Kathleen Benjaminsen, RD, LDN.; Norton, MA
Marcia Difronzo, RD, LDN; Peaboday, MA
Henry Mack, ; Pembroke, MA
Roger Knysh, CDM, CFPP; Pittsfield, MA
Richard Rosenfeld, M.D., MD; Pittsfield, MA
gary shalan, md; pittsfield, MA
Lisa VanDusen, MS, RD, LDN.; princeton, MA
Rita Buhiraja, RD, LDN; Rehoboth, MA
James Perry, ; Rockport, MA
Erica Stevens, RD, LDN; Salem, MA
Carole Vecchry, RD, LDN; Salem, MA
christine gadbois, RNBC, BSN; seekonk, MA
Suman Kohlin, RD, CNSD; Shrewsbury, MA
Melanie Beach, RD; Somerville, MA
Yosefa Ehrlich, ; Somerville, MA
Andrew Smith, MD; somerville, MA
Sarah Trist, RD, LD; somverville, MA
KUMARA SIDHARTHA, MD; SOUTH DENNIS, MA
Christopher Blesso, ; Southbridge, MA
Susan Gilbert, ; Springfield, MA
Hermine Levey Weston, RN; Springfield, MA
Gabrielle Riola, RD; Springfield, MA
Erik Deede, MD; Sudbury, MA
Donna Jones, RD; Sudbury, MA
Brian Weitze, ; Tewksbury, MA
Stacia Clinton, RD; Townsend, MA
Glenn Morash, CDM, CFPP; Townsend, MA
Kathryn Butler, MEd, RD, LDN; Wakefield, MA
Irene Sedlacko, RD, LDN; Wakefield, MA
Lauren Orlando, SLP; Waltham, MA
Sara Henry, RD; Watertown, MA
Rebecca Tipton, MD; Wayland, MA
Amy Collins, MD; Wellesley, MA
Laura Winig, MBA; Wellesley, MA
Julianne Ferro, ; West Roxbury, MA
Sherrill Conna, MD retired; Westboro, MA

Katherine Sargent, ; Westborough, MA
Deborah Burkhalter, LICSW; Westhampton, MA
Paula Murphy, LICSW; Westhampton, MA
Kelly Balcourt, RD, LDN, CNSD; worcester, MA
Kristen Baskerville, RD, LDN; Worcester, MA
Kristen McEvoy, RD, LDN; Worcester, MA
Erica Weston, ; Worcester, MA
Wendy Allard, MPH, RD, LDN; Wrentham, MA

MARYLAND

Carol Heckman, RN; Annapolis, MD
Rebecca Shelley, RN, MS; Annapolis, MD
Brenda Afzal, RN, MS; Baltimore, MD
Dr. Steven Bond, ; Baltimore, MD
Marjorie Buchanan, ; Baltimore, MD
Denise Choiniere, RN; Baltimore, MD
Melanie Coffman, RN; Baltimore, MD
Ryan Coffman, MPH, CHES, CTTS; Baltimore, MD
Rachel DeMunda, HEM, CHMM; Baltimore, MD
Jennifer Harrington, ; Baltimore, MD
Patrick Holmes, ; Baltimore, MD
Joan Kanner, ; Baltimore, MD
Rebecca Kanter, ; Baltimore, MD
Jeffrey Kaplan, MD; Baltimore, MD
Michaela Lindahl, NS; Baltimore, MD
Louise Mitchell, P.T.; Baltimore, MD
Keith Molesworth, ; Baltimore, MD
Leia Osbourne, BSN, RN; Baltimore, MD
Leia Osbow, RN; Baltimore, MD
Linda Pierce, LPN; Baltimore, MD
A R, ; Baltimore, MD
Rebecca Ruggles, MBA; Baltimore, MD
Jaimie Sagoskin, ; Baltimore, MD
Barbara Sattler, RN, DrPH; Baltimore, MD
Claudia Smith, PhD, MPH, RN-BC; Baltimore, MD
Deborah Smith, ; Baltimore, MD
Katherine Smith, ; Baltimore, MD
Robin Spence, RD, LDN; Baltimore, MD
Susan Woodman, ; Baltimore, MD
Frank Weinberg, ; Bel Air, MD
Marilyn Guterman, RN; Bowie, MD
Idayert Saidfashina, ; Bowie, MD
Lindie McDonough, ; Catonsville, MD
Penelope Paul, RN; Catonsville, MD
Kim Rencewicz, ; Catonsville, MD
Rob Rencewicz, ; Catonsville, MD
Denise Pudinski, ; Chester, MD
carol bowman, md; churchville, MD
Laura Evans, RN, MPH; Columbia, MD
Katherine McCune, RN, CNM, MS; Dickerson, MD
jane rhule, RN; edgewater, MD
Jane Rhule, ; Edgewater, MD
Hannelore Bloom, CRNP; Eldersburg, MD
Marian Condon, RN, MS; Ellicott City, MD
Marcea Cotter, RD, LDN; Ellicott City, MD
Kristi Johnson, RNC; Ellicott City, MD
Alec Anders, MD; Germantown, MD
Amanda Buchhalter, RD; Greenbelt, MD
Melissa Douglas, ; Greenbelt, MD
Ronald Keyser, MD; Hagerstown, MD
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Debra Roy, ; Laurel, MD
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Mohammed Razvi, ; Potomac, MD
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Richard Stoner, GRI; Rockville, MD
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Kathleen McPhaul, RN; Severna Park, MD
Betty Schweitzer, Retired; Severna Park, MD
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Sara McCullough, ; Silver Spring, MD
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Gaylord Clark, RN; Stevenson, MD
Margery Clark, ; Stevenson, MD
Pat Holobaugh, ; Takoma Park, MD
Darrell McCartney, ; Takoma Park, MD
Chris D'Adamo, PhD Candidate; Timonium, MD
Heather Keller, RN, BSN, CPFI; Towson, MD
Natalie Hanold, ; , MD

MAINE

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Kathy Hally, ; Blue Hill, ME
Bettie Kettell, RN; Durham, ME
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susan bickford, ; newcastle, ME
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Tyson Weems, RD; Portland, ME
Jeffrey Space, ; Rockport, ME
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MICHIGAN

Kelly Bakulski, ; Ann Arbor, MI
Marsha Benz, MPH; Ann Arbor, MI
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Martha Boggs, ; Ann Arbor, MI
Elizabeth Burt, ; Ann Arbor, MI
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Susan Hope Dundas, EMT-B; Ann Arbor, MI
Diana Dyer, MS, RD; Ann Arbor, MI
Laurie Fortlage, MS, RD; Ann Arbor, MI
Susan Garetz, MD; Ann Arbor, MI
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roger gorlewski, professor; ann arbor, MI
Larry Junck, MD; Ann Arbor, MI
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LEV LINKNER, MD; ANN ARBOR, MI
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jennifer marenghi, ; ann arbor, MI
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robert oneal, MD; ann arbor, MI
Malcolm Sickels, MD; Ann Arbor, MI
Susan Webb, CRNA, MS.; Ann Arbor, MI
Stacy Witthoff, RD; Ann Arbor, MI
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marion burgett, ; dexter, MI
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shelly winney, CMT; Grand Rapids, MI
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Helen Coverdale, retired teacher; Portage, MI
Deborah Russell, RN,FNP; Portage, MI
Heather Snow, ; Portage, MI
Miriam Scherrer, physician assistant (PA-C); Richland, MI
patricia Butler, RN, CDE, PhD; Saline, MI
diana Robison, rn,bsn; saline, MI
Cheryl Wuttke, MT. ASCP, SLS; Sterling Heights, MI
Margaret Smith, ; Tecumseh, MI
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MINNESOTA

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Kim Dauner, PhD, MPH; Duluth, MN
Lyndsay Guidinger, RN; Duluth, MN
Faris Keeling, MD; Duluth, MN
heather murphy, LMT; duluth, MN
Sarah Nelson, MD; Duluth, MN
Patricia Nielsen, Family Nurse Practitioner (FNP); Duluth, MN
Emily Onello, MD; Duluth, MN
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David Stephen, ; Duluth, MN

nancy sudak, MD; duluth, MN
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joel albers, pharm.d. ph.d.; Minneapolis, MN
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jody chrastek, RN MSN; minneapolis, MN
Ellen Doherty, RN, BS, CPON; Minneapolis, MN
cecelia Erickson, ; Minneapolis, MN
rachelle hansen, ; minneapolis, MN
Jeanne Harkness, RN, MSN; Minneapolis, MN
john harkness, MD; minneapolis, MN
Michelle Karsten, MD; Minneapolis, MN
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Julie Konrardy, Medical lab technician; Minneapolis, MN
Marie Kulick, MSEL; Minneapolis, MN
Tara Montgomery, MS, RD, LD; Minneapolis, MN
nellie munn, RN; minneapolis, MN
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Sheila Packwood, RD. LD.; St. Paul, MN
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Carol Scott, ; Wabasha, MN
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marsha cadwallader, BSN, MSW, LCSW; Durham, NC
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David Norton, ; Hampton, NH
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Rebecca Lockwood, ; Manchester, NH
karen chase, RN; new london, NH
MARION ROMANOFF, ; NEW LONDON, NH
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Kate Forbush, Work Comp adjuster; penacook, NH
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Kathleen Phair, LPN; Salem, NH
Elke Melody, RD, LD; Warner, NH
connie rieser, RD, LD, Registered Dietitian; Windham, NH
Brenda Ventrillo, HIM; Windham, NH

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Bonnie Wise, RN; Bogota, NJ
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Doreen Korn, AHN-BC; Glen Rock, NJ
Suzen Heeley, ; Hackensack, NJ
martin cecire, ; holmdel, NJ
Caroline Edwards, CRNP; Linwood, NJ
Sally Ringe, BSN, RN; Marlton, NJ
Susan Williams, RNC; Mouint Laurel, NJ
Andrea Racobaldo, RN; Pennsauken, NJ
Deepa Sannidhi, Medical Student; Piscataway, NJ
Mary Ann Rollano, RN; Point Pleasant, NJ
John McGowan, ; Ringwood, NJ
David Barry, ; Rutherford, NJ
Sarah Muller, MPH, RN; Scotch Plains, NJ
Regina Grazel, RN; Sewell, NJ
sandra rousso, RN; tenafly, NJ
Caroline Pope, BSN, RNC-NIC; Williamstown, NJ

NEW MEXICO

Karen Halderson, MPH, RD, CDE; Albuquerque, NM
benjamin zimmerman, ; Albuquerque, NM
jessie emerson, RN, certified clinical herbalist; santa Cruz, NM

NEVADA

Heather Bowman, ; Reno, NV
Laurel Coats, ; Sparks, NV

NEW YORK

Paula Brewer, RD, CDN; Albany, NY
helen Ruddy, NP; Astoria, NY
Dorothy Wrase Hares, RD; Baldwinsville, NY
Geraldine Dingman, ; Ballston Lake, NY
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Rosa Parris, RN; Bronx, NY
Alexandra Jamieson, Board Certified Holistic Health Counselor; Brooklyn, NY
Maureen McGowan, CSW; Brooklyn, NY
Jennifer Trotter, ; Brooklyn, NY
Erin Upton, ; Brooklyn, NY
Sanford Levy, MD; Buffalo, NY
Carolyn Bova, MSED/CAS; Burt, NY
Jean B Heady, RN; Clayton, NY
Judith Hoffmann, ; Corning, NY
Suzanne Parton-Meeder, RD CDN; Dale, NY
Frances Crosby, EdD, RN; East Amherst, NY
Carol Malley, MS; Farmingville, NY
Cecilia Mulvey, RN,PhD; Fayetteville, NY
Susan Moran, CDM, CFPP; Getzville, NY
Tina Facteau, BSN,RN,CDE; Glens Falls, NY
Kelly Moltzen, ; Harriman, NY
Cathey Falvo, MD, MPH; Hastings on Hudson, NY
William Griffin, ; Ithaca, NY
Maria Meoli, ; Kerhonkson, NY
diana orr, RN; Lagrangeville, NY
Billie Hall, ; Lake George, NY
NYS Nurses Association, ; Latham, NY
Loretta Madia, ; Lewiston, NY
Sara Hicks, APRN-BC (Nurse Practitioner); Long Beach, NY
Cathryne A. Welch, RN, EdD; Loudonville, NY
Laurel Grey, ; Martville, NY
Karen Kassen, RN; Massapequa Park, NY
Siby Thomas, RN; Nanuet, NY
Karen A Ballard, MA, RN, FAAN; New York, NY
Lolita Compas, RN; New York, NY
claire fagin, RN; New York, NY
Stephen Harnicar, Pharm.D, BCOP; New York, NY
Melaina Marion, ; New York, NY
Sherry Mathew, Pharm.D.; new york, NY
madeline naegle, ph.d rn; new york, NY
lauren parsly, Dietetic Intern; New York, NY
Lisa Yanowitz, ; New York, NY
Barbara Glickstein, RN, MPH, MS; New York, NY

Debbie Fritz, RN; Newburgh, NY
Nicole Basso, RN; Ny, NY
Thomas Lowe, RN, MPH; NYC, NY
Joan Gussow, MEd, EdD, nutrition professor; Piermont, NY
Lynn Moll, RD; Pittsford, NY
Cynthia Wallace, RD; Pittsford, NY
Lisa Gengo, ND, PAC; Port Chester, NY
Suzette Smookler, MS RD; port jefferson, NY
Wendy Harris, ; queens village, NY
Sara Fagan, Student nurse; Rochester, NY
Patricia Rochford, RN.C; Rockaway Park, NY
Bernadette Curry, RN181555; Rockville Centre, NY
nancy lofaro, ; saugerties,, NY
Susan Mantovani, RN; Sayville, NY
gerri goerke, ; scarsdale, NY
Kathleen Curtis, LPN; Schenectady, NY
E. Joyce Gould, RN, Rn, MSN; Schenectady, NY
Joan Stollberger, RD, CDE; Smithtown, NY
Jane Gengo, ; So.Salem, NY
Merry Sam, ; Spring Valley, NY
terry podolak, RD; syracuse, NY
Jeanne Finestone, ; Tuxedo Park, NY
Kelly Gaetz, RN; Upper Nyack, NY
Aurora Tansiokhian, MD; Vestal, NY
Carol Gburek, ; Warsaw, NY
Krystal Sampson-Thomas, Student; white Plains, NY
Maria Roche-Dean, MS,RN; Whitesboro, NY
Mini Varghese, RN; Yonkers, NY

OHIO

Therese Dowd, PhD,. RN; Akron, OH
Dorothy Marsh, RN< MSN; Akron, OH
Anne Smith, ; Barnesville, OH
Josefa Rangel, MD; Cincinnati, OH
Kathleen Morris, RN; Columbus, OH
Barbara Polivka, PhD, RN; Columbus, OH
Clarence Dunn, ; Euclid, OH
Rebecca McDermott, ASCP; Gibsonburg, OH
bonnie wagner, RN,BSN,MSN-director of nursing public health; greenville, OH
Rosemary Chaudry, RN, PhD, MPH; Marion, OH
Ria Smeraldi, ; North Olmsted, OH
Tari LaFountain, RPh; Oregon, OH
Nanci Shimman, ; Oregon, OH
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Lisa Lewis, RD, LD; Rocky River, OH
Marcel Hesseling, ; Sylvania, OH
Barbara Smykowski, R.N.; toledo, OH

OKLAHOMA

Dianne Miller-Boyle, NP; oklahoma city, OK

OREGON

Jenny Haag, RN; Aloha, OR
Stephanie Potts, FNP; Astoria, OR
Serena Kelly, FNP; Beaverton, OR
Mark Petersen, ; Bend, OR
david peter, md; canby, OR
Julie Ahrendt, RN; Corvallis, OR
Steve George, Licensed Massage Therapist; Corvallis, OR
John Helm, ; Corvallis, OR
KIMBERLY HOLTER, ; CORVALLIS, OR
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Jan Spencer, LCSW; Corvallis, OR
pauline billings, rn; dillard, OR
Tracy Davis, ; Dufur, OR
Rosalie Hammond, RN, FNP, PhD; Eugene, OR
Tracy Shepherd, RN; Eugene, OR
Dee Tvedt, RN, BSN, CGRN; Eugene, OR
Andrea Gough, MPH; Gresham, OR
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Cary Fardal, RD; Happy Valley, OR
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Bonnie New, MD MPH; Hood River, OR
martin donohoe, MD; Lake Oswego, OR
Nancy Ellis, RD, LD; Lebanon, OR
David Grant, MD; Medford, OR
charlotte aborn, RN, BSN; portland, OR
Kurt Beil, ND, MSOM, MPH; Portland, OR
Robert Brookshire, Physician Assistant; Portland, OR
Kevin Chatham-Stephens, MD; Portland, OR
Eecole Copen, MS, RD; Portland, OR
Erin Dawson, RD, LD; Portland, OR
Jacque DeVore, RD, MPH; Portland, OR
Aleta Dunne, ; Portland, OR
Karen Erde, MD; Portland, OR
Angela Gerrard, RN; Portland, OR
Debora Goldstein, RN; Portland, OR
Marceline H. Gearry, ; Portland, OR
Donna Hammar, FNP, RN; Portland, OR
Laura Hanks, PA-C; portland, OR
Mary Lou Hennrich, ; Portland, OR
Susan Katz, MD; Portland, OR
Teresa Keaane, NP; Portland, OR
Jacob Klein, RN, BSN; Portland, OR
Marc Lewis, RN; Portland, OR
Barbara Martin, PA-C; Portland, OR
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Patricia Murphy, ND, LAc; Portland, OR
Tania Neubauer, ND; Portland, OR
Marylou Noble, Licensed Professional Counselor;

Portland, OR
Carolyn Parchinsky, RN; Portland, OR
john Pearson, MD Or 10935; Portland, OR
Jenny Pompilio, MD, MPH; Portland, OR
Jeanean Rauch, RN; Portland, OR
Annie Robb, RN; Portland, OR
Kellie Schenk, MD; Portland, OR
Catherine Thomasson, MD; Portland, OR
Maye Thompson, RN, PhD; Portland, OR
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Stacey Williams, MPH; Portland, OR
kimberly amy zeigenfuse, RN; portland, OR
Linda Pesanti, retired registered nurse;
Saint Helens, OR
James A. Auerbach, M.D., MD; Salem, OR
Andrew Harris, MD; Salem, OR

PENNSYLVANIA

barsky andy, CDM; allentown, PA
Ruth McDermott-Levy, PhD, RN; Berwyn, PA
Danielle Hamilton, ; broomall, PA
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Feargal Roche, ; Havertown, PA
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Michele Ondeck, MEd, RN; McKeesport, PA
Elizabeth Ann Gatti, RNC; Monroeville, PA
Alexia Chororos, ; Narberth, PA
Diane Ferguson, RN, MSN; Ono, PA
Lucille DiCampli, ; Phila, PA
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Asher Barkon, CDM, CFPP; Philadelphia, PA
Rebecca Brichta, ; Philadelphia, PA
Shelley Chamberlain, RD,LDN; philadelphia, PA
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Allegra Gordon, MPH; Philadelphia, PA
patricia harner`, MS; Philadelphia, PA
Erin Kroll, BS; Philadelphia, PA
Myriah Lipke, MA; Philadelphia, PA
Sara Lis, RN; Philadelphia, PA
Dianne McChesney Moore, MS, MSW;
Philadelphia, PA
Kameela Miller, RNC; Philadelphia, PA
Dianne Moore, ; Philadelphia, PA
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Nathan Samras, ; Philadelphia, PA
Abbie Santana, MSPH; Philadelphia, PA
Robert Stein, ; Philadelphia, PA
Howard Sudak, MD; Philadelphia, PA
John Wierzbowski, MS, MPH; philadelphia, PA
Judith Focareta, RN, MEd; Pittsburgh, PA
Marian Pokrywka, CIC; Pittsburgh, PA
Mary Vandivier, BS ElEd/ECEDirector; Pittsburgh, PA
Christine Weinberger, MD; Pittsburgh, PA
Stanley Weinberger, MD; Pittsburgh, PA
Lynn Zakreski, Psychology, MA;
Plymouth Meeting, PA
Tamara Almquist, BS Biology; Pocono Summit, PA
Amy Heins, RN, BSN, CIC; Reading, PA
Renee Smith, RN, MS, CPAN, CAPA; Sunbury, PA
Mallory Reed, ; West Reading, PA
John Kosisky, Director / Nutritional Services;
Wilkes-Barre, PA
elizabeth keech, PhD,RN; Wynnewood, PA
Donna Novak, RN, MSN, CRNP; Yardley, PA

RHODE ISLAND

Sandra Delack, RN; North Kingstown, RI
Brian Nguyen, MA, MD; Providence, RI

SOUTH CAROLINA

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West Columbia, SC

TENNESSEE

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TEXAS

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Qin Shen, ; Bellevue, WA
Deborah Alley, ; Bothell, WA
Nancy Boyer, ; Bothell, WA
Kim Griffin, RN, BSN, MNc; Bothell, WA
Marcy Johnson, Dietetics graduate student; Bothell, WA
Gail Richards, ; Bothell, WA
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Travis Sherwood, ; Seattle, WA
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Lana Tyer, Rn; Seattle, WA
Catherine Webb, ; Seattle, WA
Jenna Umbriac, dietetic student; Shoreline, WA
Maria Umbriac, ; Shoreline, WA

Melissa Murphy, RN, BSN; Spanaway, WA
Julie Postma, PhD RN; Spokane, WA
Nancy Picou, LPN; Tacoma, WA
Bradley Thompson, RN; Tacoma, WA
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stan freidberg, MD; Vancouver, WA
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Joan Beads, ; , WA

WISCONSIN

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Sandy Panzer, RN MSN; Appleton, WI
Karlyn Raddatz, BA, RN-BSN; Appleton, WI
Allison Weyenberg, ; Appleton, WI
Amy Miller, RD, CD; Black Earth, WI
patricia Finder-Stone, RN,MS, RN, MS; De Pere, WI
Tara Wood, PharmD; Fennimore, WI
Judith Stadler, RD; Fitchburg, WI
Jesse Charles, MD candidate; Green Bay, WI
Lori Hartz, MS, RD; Greenville, WI
Lillian Nordin, FNP; Holmen, WI
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Christine Immel, D.T.R.; Kewaskum, WI
Kathryn Lammers, MS, RN; LaCrosse, WI
Diane Cozzi, MSN, RN; Lake Geneva, WI
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deborah burns, ; Madison, WI
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Patrice Udelhofen, NP; Madison, WI
sherry grandaw, ; marinette, WI
Sue Meyer, RN; Marshfield, WI
Frances Stahl, MS, LCSW; Menasha, WI
Mary Blakewell, ; Neenah, WI
Betty Koepsel, RN, MSN; Oconomowoc, WI
Belinda DeGoey, BSN; Oshkosh, WI
patty Kandiko, Public Health Nurse; Oshkosh, WI
mary vils, MS, ATC; oshkosh, WI
Arlene McEntegart, Nurse Practitioner; Racine, WI
Ellen Martin, PT; Random Lake, WI
sue wright, rn; south range, WI
Gail Baldwin, MD; Superior, WI
Lois Taylor, MA, RN; Trempealeau, WI
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Wauwatosa, WI
Laura Grant, RN; West Bend, WI
Donna Groth, RN; West Bend, WI
Doug Petsch, sales; West Bend, WI
Jan Path, RN BSN; Wilton, WI
Paulette Stoltzmann, RN; Winnebago, WI
Mary Jo Turner, RN, Public Health Nurse;
Winnebago, WI

WEST VIRGINIA

Rebecca Foster, RD; Clarksburg, WV
Barbara Hartman, MS, RD, LD; Kearneysville, WV
Kendra Stoen, MS, RD; Morgantown, WV

WYOMING

Bonita Maddex, RD; Jackson, WY

Healthy Food in Health Care Pledge

This Healthy Food in Health Care Pledge is a framework that outlines steps to be taken by the health care industry to improve the health of patients, communities and the environment.

As a responsible provider of health care services, we are committed to the health of our patients, our staff and the local and global community. We are aware that food production and distribution methods can have adverse impacts on public environmental health. As a result, we recognize that for the consumers who eat it, the workers who produce it and the ecosystems that sustain us, healthy food must be defined not only by nutritional quality, but equally by a food system that is economically viable, environmentally sustainable, and supportive of human dignity and justice. We are committed to the goal of providing local, nutritious and sustainable food.

Specifically, we are committed to the following healthy food in health care measures for our institution. We pledge to:

Increase our offering of fruit and vegetables, nutritionally dense and minimally processed, unrefined foods and reduce unhealthy (trans and saturated) fats and sweetened foods.

Implement a stepwise program to identify and adopt sustainable food procurement. Begin where fewer barriers exist and immediate steps can be taken, such as the adoption of rBGH free milk, fair trade coffee, or selections of organic and/or local fresh produce in the cafeteria.

Work with local farmers, community-based organizations and food suppliers to increase the availability of fresh, locally-produced food.

Encourage our vendors and/or food management companies to supply us with food that is produced in systems that, among other attributes, eliminate the use of toxic pesticides, prohibit the use of hormones and non-therapeutic antibiotics, support farmer and farm worker health and welfare, and use ecologically protective and restorative agriculture.

Communicate to our Group Purchasing Organizations our interest in foods whose source and production practices (i.e. protect biodiversity, antibiotic and hormone use, local, pesticide use, etc) are identified, so that we may have informed consent and choice about the foods we purchase.

Develop a program to promote and source from producers and processors which uphold the dignity of family, farmers, workers and their communities and support sustainable and humane agriculture systems.

Educate and communicate within our system and with our patients and community about our nutritious, socially just and ecologically sustainable healthy food practices and procedures.

Minimize and beneficially reuse food waste and support the use of food packaging and products that are ecologically protective.

Report annually on implementation of this Pledge.

Signed _____ Date _____

Health Care Without Harm

NORTHEAST

Baystate Health, MA
Berkshire Medical Center, MA
Bon Secours Health System, Warwick, NY
Bon Secours Charity Health System:
Good Samaritan Hospital of Suffern, NY
Community Hospital, Port Jervis, NY
Boston Medical Center, Boston, MA
Brattleboro Memorial Hospital, VT
Bridgeport Hospital, Bridgeport, CT
The Center for Discovery, NY
Cheshire Medical Center, Dartmouth-Hitchcock, Keene, NH
Cooley Dickinson Hospital, MA
Covenant Health Systems:
Maristhill Nursing & Rehabilitation Center, MA
Mary Immaculate Health/Care Services, MA
St. Mary's Health System, MA, including:
St. Mary's Residences
St. Mary's d'Youville Pavilion
St. Mary's Regional Medical Center
St. Andre Health Care Facility, ME
St. Joseph Healthcare Nashua, NH
St. Joseph Manor Health Care, MA
St. Mary Health Care Center, MA
St. Mary's Villa, PA
Youville Hospital & Rehabilitation Center, MA
Youville House, MA
Youville Place Assisted Living Residence, MA
Dartmouth-Hitchcock Medical Center, NH
Fairview Hospital, MA
Fletcher Allen Health Care, VT
Lawrence and Memorial Hospital, CT
Lincoln County Healthcare:
St. Andrews Hospital & Healthcare Center, ME
Miles Memorial Hospital, ME
Littleton Regional Hospital, NH
Memorial Sloan-Kettering Cancer Center, NY
Metro West Medical Center:
Framingham Union Hospital, MA
Leonard Morse Hospital, MA
Mid Coast Health Services:
Mid Coast Hospital, ME
Mid Coast Senior Health Center, ME
Thornton Oaks Retirement Community, ME
Milford Regional Medical Center, MA
Mt. Ascutney Hospital & Health Center, VT
New Milford Hospital, CT
Northeastern Vermont Regional Hospital, VT
Olean General Hospital, NY
The Orchard Nursing and Rehabilitation Centre, NY
Parkview Adventist Medical Center, ME
Porter Medical Center, VT
Regeis Care Center, NY
Rutland Regional Medical Center, VT
Schervier Nursing Care Center, NY
Shriners Hospital for Children, MA
Southwestern Vermont Health Care, Bennington, VT
Spaulding Rehabilitation Hospital, MA

MID-ATLANTIC

Abington Memorial Hospital, PA
Anne Arundel Medical Center, MD
Baltimore Washington Medical Center, MD
Bon Secours Baltimore Hospital, MD
Calvert Memorial Hospital, MD
Carroll Hospital Center, MD
Children's Hospital of Pittsburgh of UPMC, PA
Christiana Care Health Systems:
Christiana Hospital, DE
Wilmington Hospital, DE
Cooper University Hospital, NJ
Geisinger Health System, PA
Georgetown University Hospital, DC
Hackensack University Medical Center, NJ
Holy Redeemer Health System, PA
Howard County General Hospital, MD
LifeBridge Health:
Courtland Gardens Nursing & Rehabilitation Home, MD
Levindale Hebrew Geriatric Center and Hospital, MD
Northwest Hospital, MD
Sinai Hospital, MD
Long View Nursing Home, MD
Mercy Medical Center, MD
Mt. Washington Pediatric Hospital, MD
Northwest Health and Rehab Center, MD
Shady Grove Adventist Hospital, MD
Sinai Hospital, MD
Thomas Jefferson University Hospital, PA
Union Hospital of Cecil County, MD

University of Maryland Medical Center, MD
Washington Adventist Hospital, MD

SOUTHEAST

Baptist Health South Florida:
Baptist Hospital, FL
Doctors Hospital, FL
Homestead Hospital, FL
Mariners Hospital, FL
South Miami Hospital, FL
Bon Secours Hampton Roads:
DePaul Medical Center, VA
Mary Immaculate Medical Center, VA
Maryview Medical Center, VA
Bon Secours Richmond Health System:
Bon Secours St. Mary's Hospital, Richmond, VA
Memorial Regional Medical Center, Mechanicsville, VA
Richmond Community Hospital, VA
St. Francis Medical Center, Midlothian, VA
Bon Secours St. Francis Health System:
St. Francis Downtown, SC
St. Francis Eastside, SC
Children's Healthcare of Atlanta, GA
INOVA Alexandria Hospital, VA
Mission Hospitals, NC
Reston Hospital Center, VA
St. Mary's of Campbell County, Lafollette, TN

MIDWEST

Adventist Bolingbrook Hospital, IL
Advocate Christ, IL
Advocate Health Care:
Advocate Bethany Hospital, IL
Advocate Christ Medical Center, IL
Advocate Illinois Masonic Medical Center, IL
Advocate Lutheran General Hospital, IL
Advocate South Suburban Hospital, IL
Advocate Trinity Hospital, IL
Good Samaritan Hospital, IL
Good Shepherd Hospital, IL
Altom Memorial Hospital, IL
Aurora Health Care:
Aurora BayCare Medical Center, WI
Aurora Lakeland Medical Center, WI
Aurora Medical Center, Hartford, WI
Aurora Medical Center, Kenosha, WI
Aurora Medical Center, OshKosh, WI
Aurora Medical Center, Two Rivers, WI
Aurora Memorial Hospital of Burlington, WI
Aurora Psychiatric Hospital, WI
Aurora Sheboygan Memorial Medical Center, WI
Aurora Sinai Medical Center, WI
Aurora St. Luke's Medical Center, WI
Aurora St. Luke's South Shore, WI
Aurora West Allis Medical Center, WI
Bartels Lutheran Retirement Community, IA
Bon Secours Kentucky Health System:
Our Lady of Bellefonte Hospital, Ashland, KY
Beaumont Hospital, Grosse Pointe, MI
Borgess Medical Center, Kalamazoo, MI
Bronson Methodist Hospital, MI
Cancer Treatment Center of America at Midwestern Regional Medical Center, IL
Cass County Memorial Hospital, IA
Chelsea Community Hospital, MI
Children's Hospitals and Clinics of Minnesota, MN
Cleveland Clinic:
Cleveland Clinic Main Campus, OH
Euclid Hospital, OH
Fairview Hospital, OH
Hillcrest Hospital, OH
Huron Hospital, OH
Lakewood Hospital, OH
Lutheran Hospital, OH
Marymount Hospital, OH
South Pointe Hospital, OH
Drake Center, OH
Galesburg Cottage Hospital, IL
Hennepin County Medical Center, MN
Henry Ford Health System, MI
Henry Ford West Bloomfield, West Bloomfield, MI
Hopedale Medical Complex, IL
HospiceCare Inc., WI
Illini Community Hospital, IL
Immaculate Heart of Mary, Monroe, MI
Marquette General Hospital, MI
Memorial Hospital of South Bend, IN
Mercy Medical Center, IA
Metro Health Hospital, MI
Northern Michigan Regional Health System, Petoskey, MI
Pana Community Hospital, IL

Ridgeview Medical Center, Waconia, MN
River Falls Area Hospital, WI
Sacred Heart Hospital, Eau Claire, WI
Sparrow Health System, Lansing, MI
Spectrum Health System, MI
St. Elizabeth Healthcare:
St. Elizabeth Covington, KY
St. Elizabeth Medical Center, KY
St. Elizabeth North, KY
St. Elizabeth Florence, KY
St. Elizabeth Ft. Thomas, KY
St. Elizabeth Grant County, KY
St. Joseph Mercy Health System, MI
St. Luke's Hospital, MN
St. Nicholas Hospital, WI
St. Vincent Hospital, WI
Swedish Covenant Hospital, IL
Valley West Community Hospital, IL
Waukesha Memorial Hospital, WI
Weiss Memorial Hospital, IL
West Hospital, IA
Winona Health, MN

NORTHWEST

Cascade Healthcare Community:
St. Charles Medical Center, Bend, OR
St. Charles, Redmond, OR
Children's Hospital and Regional Medical Center, WA
Good Shepherd Medical Center, OR
Island Hospital, WA
Kaiser Atrium Cafe, OR
Kaiser Sunnyside Medical Center, OR
Kootenai Medical Center, ID
Legacy Health System:
Legacy Emanuel Hospital & Health Center, OR
Legacy Emanuel Children's Hospital, OR
Legacy Good Samaritan Hospital &
Medical Center, OR
Legacy Meridian Park Hospital, OR
Legacy Mount Hood Medical Center, OR
Legacy Salmon Creek Hospital, OR
MultiCare Health System:
Tacoma General Hospital, WA
Mary Bridge Children's Hospital, WA
Allenmore Hospital, WA
Covington Outpatient Center, WA
Northwest Hospital & Medical Center, WA
Oregon Health and Science University Hospital, OR
Overlake Hospital Medical Center, WA
Shriners Hospital for Children, OR
St. Luke's Wood River Medical Center, ID
St. Patrick Hospital and Health Sciences Center, MT
Swedish Medical Center:
Swedish Cherry Hill, WA
Swedish First Hill, WA
Swedish Ballard, WA
University of Washington Medical Center, WA

CALIFORNIA

Bakersfield Memorial Hospital, CA
Hoag Memorial Hospital Presbyterian, Newport Beach,
CA
John Muir Health System
John Muir Health, Concord Campus, CA
John Muir Health, Walnut Creek Campus, CA
John Muir Behavioral Health Center, CA
Kaiser Permanente, including 32 facilities in CA, CO, GA,
HI, OH, OR, WA
Sharp Coronado Hospital, CA
St. Joseph Health System
Santa Rosa Memorial Hospital (3 campuses), CA
Petaluma Valley Hospital, CA
St. Jude Medical Center, CA
St. Joseph Hospital, CA
St. Mary Medical Center, CA
UCSF Medical Center, San Francisco, CA
Washington Hospital Healthcare System, CA

SOUTHWEST

Catholic Healthcare West System Facilities including 40
facilities in CA, NV, AZ
Covenant Medical Center, St. Joseph Health System, TX
Cypress Creek Hospital, TX
Grand River Medical Center, CO
Spring Branch Medical Center, TX

JOINT STATEMENT FOR THE RECORD
Subcommittee on Health, Committee on Energy & Commerce
U.S. House of Representatives

For the Hearing On Antibiotic Resistance And The Use Of Antibiotics In Animal Agriculture

July 14, 2010

As organizations committed to protecting patients, public health, animal health, and food safety, we wish to submit this written testimony to express our concern about the misuse of antibiotics in agriculture and our strong support for policies, including the Preservation of Antibiotics for Medical Treatment Act (PAMTA, H.R. 1549, S. 619), that will institute a public health approach to antimicrobial use in animals. We commend the Subcommittee on Health for holding hearings to examine the growing public health threat of antibiotic resistance, including today's hearing specifically on the contribution of animal agriculture to the problem. We urge the Subcommittee to follow these hearings with prompt legislative action to greatly reduce or eliminate the non-judicious use of important antibiotics in animal feed and water.

Our combined memberships include the country's foremost scientific and medical experts and represent more than nineteen million concerned Americans and health professionals. Our position is based on objective health interests and concerns that dangerous drug-resistant infections are rapidly increasing in hospitals and community settings, causing unnecessary human suffering and adding to the economic burden of U.S. healthcare costs as well as jeopardizing the effectiveness of treatments for sick animals.

The development of antibiotics to treat life-threatening infections has been one of the most notable medical achievements of the past century. Physicians, healthcare professionals, and public health and food safety advocates are greatly concerned about the growing body of scientific evidence demonstrating that antimicrobial drug use in livestock and poultry contributes to the spread of drug-resistant bacteria to people. Drug-resistant organisms are plaguing Americans, including otherwise healthy individuals, in healthcare settings and communities across the country. We are pleased that these concerns finally are being recognized and that Congress is poised to consider solutions to forestall epidemics of untreatable infections.

Specifically, we support phasing out the use of antimicrobial drugs for growth promotion and feed efficiency, much more limited use for disease prevention, and requiring that all uses of these drugs be carried out under the supervision of a veterinarian and within the boundaries of a valid veterinarian-client-patient relationship – which we expect will end over-the-counter sales of tons of antimicrobial drugs annually. We support clearly defining the limited instances where antibiotics may be used judiciously in food animals for purposes of disease prevention and control and are eager to work with policymakers to ensure that any legislation considered is fully protective of public health. We urge Congress to enact a new antimicrobial policy that is mandatory, retroactive to already-approved drugs, and enforceable, in order to best guarantee a significant reduction in non-judicious antibiotic use.

While the U.S. Food and Drug Administration recently issued a draft guidance that suggests agreement with some of these principles, we are concerned that the agency has not clearly indicated to what extent preventative uses are encompassed in the guidance, nor has it laid out a timeline for action or a commitment to regulatory steps. It is therefore imperative that Congress act swiftly to protect public health. PAMTA is a sound science-based approach that is backed up by scores of scientific and medical publications and will protect the health of every American.

By enacting PAMTA, Congress would eliminate non-judicious uses of antimicrobial drugs, including for purposes of growth promotion, feed efficiency and non-judicious disease prevention which have been practiced in animal agriculture for several decades. This would better protect the public against resistant infections and preserve the power of existing antibiotics. In addition, we urge Congress to ensure long-overdue veterinary supervision of all antibiotic uses in animals and end over-the-counter sale of antibiotics for animal agricultural uses. The sale of antibiotics for use in human medicine requires a prescription; there is no reason to permit a lower standard for agricultural purposes where considerably more antibiotic drugs are used annually. Finally, we would urge Congress to examine whether veterinarians should be permitted to sell antibiotics for a profit. Such a marketing paradigm fosters inherent conflicts of interest that could lead to non-judicious uses of these precious drugs. In 1995, Denmark put significant limits on the ability of veterinarians to profit from the sale of antibiotics in food animal production. This led directly to a reduction in total usage of antibiotics, especially tetracyclines.

Adopting such policies would reflect the concerns of a broad consensus of the scientific, medical, public health and international health communities. Such consensus is buttressed by the actions of expert bodies and governments. For example:

- Since 2002, the World Health Organization (WHO) has called upon all nations to terminate or rapidly phase out the use of antimicrobial growth promoters in food animals.

- In 2003, the Institute of Medicine (IOM) of the National Academies of Science called on the FDA to ban the use of antimicrobials for growth promotion in animals, if those drugs were also used in human medicine.

- In 2006, the European Union banned non-therapeutic use of antimicrobials, because such use was found to raise food safety concerns, and the ban was instituted to protect against further development of antimicrobial resistance.

We recognize that phasing out of antibiotics for non-judicious uses in animals will require changes in the agricultural industry. But protection of the public's health must come first, and the phase-out can be conducted in a way that minimizes costs to the agriculture industry. Farmers in Europe have adapted to such a policy without undue disruption of production or increased consumer costs; the United States can learn from that experience while also protecting American lives. In addition, the U.S. Department of Agriculture has recognized that various production methods used in the United States today are viable alternatives to non-judicious antimicrobial uses and such alternatives are employed with little negative – or even with somewhat positive – economic impact to producers.

We urge you to advance scientifically sound policies to phase out growth promotion and feed efficiency uses, and to strictly manage a narrow set of prophylactic uses while mandating veterinary-patient relationships and eliminating the over-the-counter sale of antibiotics for use in animals.

We remain committed to working with the members of the Energy and Commerce Committee to design these approaches in ways that will best protect the lives and health of both humans and animals.

Alliance for the Prudent Use of Antibiotics

American Academy of Pediatrics

American Association of Critical-Care Nurses

American Medical Association

American Nurses Association

American Public Health Association

American Society of Health-System Pharmacists

APIC—Association for Professionals in Infection Control and Epidemiology, Inc.

Consumers Union

Food Animal Concerns Trust

Humane Society of the United States

Infectious Diseases Society of America

Institute for Agriculture and Trade Policy

Keep Antibiotics Working

Michigan Antimicrobial Resistance Reduction Coalition

National Foundation for Infectious Diseases

Society of Infectious Disease Pharmacists

The Pew Charitable Trusts

Union of Concerned Scientists

KEEP ANTIBIOTICS WORKING
The Campaign to End Antibiotic Overuse
www.KeepAntibioticsWorking.com

STEERING COMMITTEE
Center for Science in the Public Interest
Environmental Defense
Food Animal Concerns Trust
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Institute for Agriculture and Trade Policy
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National Catholic Rural Life Conference
Natural Resources Defense Council
Physicians for Social Responsibility
Safe Tables Our Priority (S.T.O.P.)
Sierra Club
Union of Concerned Scientists
Waterkeeper Alliance

Keep Antibiotics Working

Statement for the Record

House of Representatives,
Health Subcommittee to the Energy and Commerce Committee
Hearing on the Public Health Risk from the Use of Antibiotics in Food-Producing Animals

Wednesday, July 14, 2010, 2:00 PM

Keep Antibiotics Working appreciates the attention that this committee is giving to the public health problem of antimicrobial resistance resulting from the use of antibiotics in food producing animals. Keep Antibiotics Working (KAW), a coalition of health, consumer, agricultural, environmental, humane and other advocacy groups, whose organizations have more than ten million members, is dedicated to eliminating this major cause of antibiotic resistance.

Antibiotic resistance has long been considered by the Centers for Disease Control (CDC) one of the "most pressing public health problems."[i] People already die from infections untreatable with existing antibiotics. More – perhaps many, many more – will die in years to come. This critical public health problem therefore requires a comprehensive approach that addresses *all sources* of resistance affecting human health.

Summarizing four decades of scientific research, the U.S. Food and Drug Administration recently identified an important part of the problem: the injudicious use of antibiotics in food animal production[ii].

The age of miracle antibiotics may be coming to an end. Before even more people die of resistant infections, KAW therefore advocates that Congress at long last address this crisis, and, in particular, support the scientifically sound approach found in H.R. 1549, The Preservation of Antibiotics for Medical Treatment Act (PAMTA).

PO Box 14590 • Chicago, IL 60614-0590
PHONE: 773-525-4952 • FAX: 773-525-5226 • E-MAIL: information@KeepAntibioticsWorking.com

Yes, the FDA has identified the need to act. But it has failed to take any action steps, or, even to identify what steps it intends to take to address this critical public health problem. Because of the FDA's historic failure to act, Congress must step in and assure by passing PAMTA that FDA moves forward to protect public health.

Antibiotic-resistant infections: Major threats to food safety and public health

As is well known to the medical community, we face an urgent crisis of antibiotic resistance. Once considered miracle drugs, antibiotics are becoming less and less effective at treating infections and disease. Many Americans have died or fallen seriously ill due to antibiotic-resistant bacteria. When initial antibiotics don't work, it can mean several days of unnecessary pain and suffering while doctors figure out another drug is needed. Treating a patient with an ineffective drug also can give infections the chance to progress to more serious illness. For cases where none of the available antibiotics work, resistance becomes a matter of life and death. In addition to rendering drugs ineffective, resistant strains are often more virulent than their susceptible counterparts – causing more serious disease, longer hospitalizations, and driving higher healthcare costs.

Antibiotic resistance is particularly worrisome in terms of food safety. Half of all human Campylobacter infections are drug resistant, as are one in five Salmonella infections[iii]. Salmonella and Campylobacter, the most common sources of food borne illnesses in the United States, account for well over a million resistant infections in this country each year[iv]. It is not unusual for Salmonella to be resistant to many drugs at once, as was the case for several outbreaks linked to ground beef last year. Getting sick with multidrug resistant strains of Salmonella can "increase the risk of hospitalization or possible treatment failure in infected individuals"[v].

Antibiotic resistance is not a problem only for humans. The bottom line of antibiotic resistance—harder to treat diseases and higher medical costs—is also true for veterinary medicine.

Antibiotic resistance results from antibiotic use

Microorganisms exist in an interconnected ecosystem and travel back and forth among humans, animals, and other elements in the environment. Exposure to antibiotics selects for those bacteria that can withstand the drug. Resistant organisms are most encouraged in settings where antibiotics are heavily used—primarily human medicine, veterinary medicine, and food animal production. But antibiotic-resistant microorganisms generated in the guts of pigs in the Iowa countryside, for example, don't stay on the farm. They can be transmitted to humans in at least three ways: carried on meat or poultry; colonizing farm workers who transmit them into the community; or moving through water and soil, which can lead to the contamination of fresh produce.

When the antibiotics used in raising food animals such as pigs are the same (or more precisely, in the same classes) as those used in doctors' offices, bacteria from the pigs will be impervious to therapies based on the drugs[vi].

The fundamental approach to prolonging the effectiveness of drugs is to curb unnecessary uses. Every sector needs to accept responsibility and curb its own unnecessary antibiotic use.

The medical profession has stepped up to the plate and identified and attempted to address the issue by establishing guidelines against unnecessary uses, like treatment of viral diseases, and aggressively seeking to reduce prescriptions for those uses. Periodically, it evaluates the effectiveness of its initiatives.

To date, the veterinary and industrial agriculture communities lag far behind the human medical community in taking similar steps to reduce unnecessary use. Instead it has spent its energies in minimizing or denying the problem.

Production agriculture's contribution to the problem

As it turns out, food animal production uses the lion's share of the antibiotics in the United States—about 70 percent of the total. The estimates include drugs used in only three livestock sectors—poultry, swine, and beef cattle—and only for purposes other than treating sick animals—nontherapeutic purposes like growth promotion and routine disease prevention. All of these antibiotics, among them penicillins, tetracyclines, and erythromycin—are in classes of drugs used in human medicine[vii] Most of these drugs are delivered to animals mixed in their feed.

Why do animal producers use such huge quantities of valuable drugs when most of the antibiotics are not used to treat disease? In part, because growth promotion and feed efficiency uses are thought to improve the bottom line even in healthy animals. But also because drugs are needed to compensate for crowded, stressful, and unhygienic conditions characteristic of many animal production operations.

The link between animal production and reduced efficacy of human drugs

In light of the enormous use in production agriculture of exactly the same drugs used in human medicine, it is difficult to imagine a credible scenario under which resistant bacteria generated in the billions of animals we grow for food would not find their way to human populations and erode the effectiveness of our antibiotic arsenal. And indeed a mountain of scientific studies now demonstrates that that is the case.

The list of antibiotic-resistant pathogens originating in animals is long. It includes the foodborne illnesses mentioned above, caused by Campylobacter and Salmonella. Resistant urinary tract infections, which can be caused by a number of different animal-associated bacteria, including E. coli, have also been linked to animal sources. Microorganisms originating in animals are also often associated with bloodstream infections that affect hospitalized patients. Resistance in Campylobacter and Salmonella is associated with increased bloodstream infections, increased hospitalization, and increased death[viii]. And the list continues to grow.

We have only recently learned that livestock can be an important source of life-threatening methicillin-resistant *Staphylococcus aureus* (MRSA). In Europe, a strain of MRSA responsible for 20 percent of human MRSA infections in the Netherlands[ix] has been shown to be transmitted from pigs to farmers and their families, veterinarians, and hospital staff[x]. The pig-associated strain of MRSA has now been found in Canada[xi] and in the United States[xii].

Importantly, the list of resistant bacteria themselves traceable to animals does not convey the full scope of the problem. Bacteria are promiscuous. They can acquire bits of DNA, including resistance traits, from unrelated bacteria. This means that the traits that originate in animal guts might move through the microbial ecosystem to confer resistance on bacteria not of animal origin. In addition, bacteria are known to harbor large circles of DNA that carry ten or more resistance traits[xiii]. In these circumstances, the use of one antibiotic, say penicillin, can simultaneously drive up the levels of resistance to other antibiotics, like tetracycline, gentamicin, and cephalosporins.

The literature in this arena is voluminous and the conclusion is clear: antibiotic overuse in agriculture—just as in human medicine—is undercutting the efficacy of important human therapies and generating more virulent pathogens.

The recent FDA Draft Guidance Document #209 provides an overview of 40 years of studies on this topic[xiv] and finds that independent reviews of the data have consistently found a risk to public health and have repeatedly recommended reducing overuse.

Reducing antibiotic use

As long as the massive use of antibiotics continues, animals will remain an important source of resistant pathogens, dangerous to both animals and humans. The straightforward solution to the problem is to reduce the use of antibiotics in animal production and thereby diminish the pool of resistant organisms and traits.

Fortunately, the largest amounts of antibiotics in food animal production are used for growth promotion, feed efficiency, and routine disease control, uses that can be eliminated without damage to animal health or unacceptable increases in animal production costs or consumer meat prices.

As documented in the scientific literature, these uses can be reduced or eliminated with modern management practices. The viability of such practices has been demonstrated in a variety of different kinds of animal agricultural operations. On the more industrialized side, Tyson, Inc., a major poultry grower and retailer, was able to develop systems for all of its retail chicken that used no antibiotics at all. On the more niche side, cattle grown out-of-doors and fed primarily grass rarely need antibiotics at all. Many American producers, like Laura's Lean Beef, Niman Ranch, and Coleman Natural, are thriving in the marketplace selling beef and pork produced without antibiotics.

A 2009 report from the USDA Economic Research Service looking at changes in U.S. agriculture supported the notion that antibiotic use in agriculture could be reduced without

significant costs to producers[xv]. The USDA confirmed that large farms are more likely than small farms to use antibiotics in feed but noted that the benefits of this use is limited to certain stages of production, particularly pig nurseries. For other stages of production like finisher pigs, there were few benefits. The USDA also found that practices such as increased sanitation and vaccination could be substituted for antibiotics.

Data from Europe also support the feasibility of reducing antibiotic use even in intensely industrial poultry and swine systems. In 1999, Denmark, the world's leading pork exporter, ended all use of antimicrobial growth promoters without reducing the productivity of its livestock sector[xvi].

Policy recommendation

Because as mentioned above, reductions in the use of antibiotics can often be achieved by managing animals and their feeds better, production agriculture represents a golden opportunity to reduce the pressure driving up resistance traits in the microbial ecosystem.

A sensible and protective two-part policy would:

a) Reduce antibiotic use wherever possible in animal production by establishing and enforcing clinical practice guidelines in veterinary medicine

b) Review, and where supported by the evidence, cancel the use of those antibiotics also used in human medicine (so-called medically important drugs) in animal agriculture for non-therapeutic purposes like growth promotion, feed efficiency, and routine disease prevention. The classes of medically important drugs are penicillins, tetracyclines, sulfonamides, lincosamides, streptogramins, aminoglycosides, and macrolides.

Such a policy would lead to substantial reductions in antibiotic use without depriving producers of antibiotics to treat sick animals. It is important to point out that a number of antibiotic-like drugs are not used in human medicine, and that, under this approach, these drugs would be available to producers for any purpose including feed efficiency or routine disease prevention.

To accomplish public health and food safety goals, the policy needs to be effective across the board. A level playing field will force innovation in the industry and enable producers to resist temptation to fall back on antibiotics to compensate for sloppy management practices.

Reduce through PAMTA

The FDA has the authority to cancel antibiotics that are no longer safe from a resistance point of view, but so far has used it only in the case of fluoroquinolones in poultry.

While FDA has correctly identified the problem of antibiotic overuse in its new Draft Guidance Document #209, the document gives no indication that FDA is taking steps to actually prohibit antibiotic overuse. There is nothing in the new draft policy by the FDA that

even suggests that the FDA has overcome the legal and institutional barriers that have long blocked action on this important public health issue. The policy itself falls short because it only recommends reduction of antibiotics used for growth promotion. The FDA guidance does describe a vision of appropriate preventative use but the FDA has no authority to regulate veterinary practice to the extent that would be necessary to require that this vision be followed. {Once drugs are on the market, and there are many more existing approvals for disease prevention than growth promotion, the FDA has very little ability to change how they are being used.}

So even if the current policy were to be implemented sometime in the future, the public health impact could be limited because it fails to recognize that drugs used for growth promotion can often be used in the exact same manner as drugs used for disease prevention. There is no benefit to be gained from continuing to use the same drugs in the same manner but calling it disease prevention instead of growth promotion. The FDA's push for voluntary changes by drug manufacturers is highly likely to result in only this type of cosmetic change and is unlikely to lead to real reductions in use and the subsequent reductions in resistance.

The failure of the FDA to move gave impetus to the Preservation of Antibiotics for Medical Treatment Act (PAMTA) and Draft Guidance #209 does nothing to diminish the need for legislative action. This legislation would require the FDA to review antibiotics used in animal agriculture to determine whether they put public health at risk by leading to increased resistance and to withdraw from the market in a timely manner those drugs that cannot be shown to be safe.

This legislation has been endorsed by over 350 organizations, including the American Medical Association, American Academy of Pediatrics, American Nurses Association, American Public Health Association, and Infectious Diseases Society of America.

Delay on antibiotics: a disadvantage in the marketplace

The European Union (EU) now has an EU-wide ban on non-therapeutic uses of antibiotics[xvii]. New Zealand[xviii], Thailand[xix], and Korea[xx] also have either enacted or will soon enact bans on certain non-therapeutic antibiotic use.

As warned in a Government Accountability Office (GAO) report from 2004[xxi], these countries also represent potential challenges to U.S. products in the global marketplace. Under the trade rules, countries can restrict imports that do not conform to certain rules, provided they adhere to those rules themselves. For example, Korea could potentially restrict imports that relied on medicated feed not allowed in Korea. The greater the number of export partners that adopt such bans, the more vulnerable our meat exports in the global marketplace. As further noted in the GAO report, if a major importer were to restrict trade from the United States because of the use of nontherapeutic antibiotics, that action would override any economic benefits of this practice.

The U.S. animal agriculture industry is at risk of following the example of the U.S. auto industry and failing to see where the market is going. Increasingly, consumers are seeking

meat from animals raised without these antibiotics. International competitors are beginning to meet this demand. In addition to protecting public health, minimizing antibiotics use in livestock can help U.S. producers add consumer value to their products, and position themselves advantageously in the global marketplace. American producers should be supported in reducing their antibiotics use.

Conclusion

Antibiotic-resistant infections are making more people sick, and keeping them sick for longer. Longer hospital stays to treat these infections are also increasing the nation's health costs—by one recent estimate adding well over $24 billion per year to the health care tab in the United States[xxii]. And, of course, more time away from work is a drag on our economy.

We have waited far too long for action to reduce the unnecessary uses of antibiotics in food animal production. While we have dithered, drugs have stopped working, new resistant diseases have emerged, old diseases have gotten worse, and people have died.

Neither can we rely on the arrival of new drugs. The unhappy truth is that there are virtually no new classes of antibiotic drugs in the pipeline[xxiii]. The discovery of new classes of antibiotics, once almost a predictable occurrence, has become frustratingly difficult in recent decades.

Even if we were able to develop a portfolio of new antibiotic drugs, we'd risk bacteria becoming resistant to them too, unless we take steps to assure they are used judiciously. We must act to preserve the continued effectiveness of today's antibiotics, or risk the age of the miracle antibiotics coming to an end.

While FDA in Guidance #209 has recognized the problem and the solution, there is nothing in the document that indicates it is ready to tackle this problem head on.

There is simply no reason to continue the profligate use of valuable antibiotics for economic purposes or to compensate for the stressful, crowded animal production facilities. The improved management practices necessary to reduce, if not avoid, antibiotic use are available and feasible. Yet, production agriculture has been unwilling to acknowledge, much less act on, this problem. We cannot tolerate this situation any longer. To protect our food supply and the public health, we must pass PAMTA.

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STATEMENT FOR THE RECORD
Subcommittee on Health, Committee on Energy & Commerce
U.S. House of Representatives
For the hearing, "Antibiotic Resistance and the Use of Antibiotics in Animal Agriculture"

July 14, 2010

Jim Slama
President
FamilyFarmed.org
Oak Park, IL

Mr. Chairman and Members of the Committee, I am Jim Slama, President of Familyfarmed.org, an organization that assists small farmer access the food marketing and distribution system. I am writing to fully support the Preservation of Antibiotics for Medical Treatment Act (PAMTA). For the past decade, FamilyFarmed.org has supported the development of local food systems. In this time, we have worked with many farmers who produce livestock, poultry, and dairy products and who do not use antibiotics for growth promotion.

Many of these farmers and ranchers are highly successful. They have rapidly growing businesses fueled in part by consumers eager to purchase naturally raised meat and dairy products. In recent months, the demand for grass-fed beef products has been very strong and some producers have been unable to keep up with the demand. And, companies like Chipotle, Whole Foods Market, Trader Joes, and others are furthering the market development for naturally raised meat and dairy products by purchasing them in high volumes.

Grass-fed livestock production is an environmentally friendly system that provides consumers with healthy, great tasting food. PAMTA will encourage even more producers to move into this niche and meet the demand for these products. Thanks for your interest in this topic.

Statement of

Robert S. Lawrence, MD

The Center for a Livable Future Professor of Environmental Health Sciences
Johns Hopkins Bloomberg School of Public Health

Director, Center for a Livable Future
The Johns Hopkins University

Hearing on

Antibiotic Resistance and the Use of Antibiotics in Animal Agriculture

Subcommittee on Health

Committee on Energy and Commerce

U.S. House of Representatives

July 14, 2010

The relationship between food animal production and antimicrobial resistance extends beyond one or two particular drugs; almost every major class of medically important antimicrobials, from penicillin to third-generation cephalosporin compounds, has been approved for use in animal agriculture (Sarmah, et al., 2006). In some cases, new drugs were licensed for agricultural use before their approval in human medicine. Resistance to these drugs was then detected before they became available to physicians for treatment of human patients, further suggesting a causal relationship between animal agriculture and resistance (Kieke, et al., 2006). Indeed, researchers have consistently found that using antimicrobials in food animal production shortens the "useful life" of existing drugs to treat both human and veterinary diseases (Smith, et al., 2002).

The current discussion of antimicrobial resistance has focused on the inappropriate prescription of drugs by physicians, and noncompliance with treatment regimens by patients. The animal agricultural industry asserts these factors as the primary cause of resistance. However, it is estimated that food animals consume as much as 70 percent of antimicrobials administered in the United States — almost 25 million pounds per year (Mellon, et al., 2001). In North Carolina alone, the quantity of antimicrobials consumed by food animals exceeds the quantity utilized in human medicine throughout the United States (Florini, et al., 2005). The use of antimicrobials in animal agriculture clearly exceeds their prescription in human medicine, suggesting the importance of food animal production's contribution to resistance.

The use of antimicrobial drugs as growth promoters in food animal production is of special concern. In these cases, drugs are typically added to feed and water at levels below those used to treat clinical infection in animals. The exposure of bacteria to lower concentrations of antimicrobial agents selects for resistance. Under these conditions, resistant strains are more likely to survive and reproduce, and, given that most bacteria reproduce every 20-30 minutes, an entire population will quickly express resistance as the susceptible strains of the bacteria are eliminated by the low-dose antibiotics (Spellberg, et al., 2008).

Furthermore, the industry asserts that, beyond growth promotion, antimicrobial drugs remain necessary for treatment, prevention, and control of pathogenic bacteria, often conflating these purposes and collectively labeling them "therapeutic use." Very few antimicrobials used in agriculture are administered as treatment for infection (Mellon, et al., 2001). Nevertheless, food animals should receive treatment for clinical disease. Furthermore, using antimicrobial drugs to control the outbreak of specific, diagnosable pathogens also merits consideration, with proper regulatory and veterinary oversight.

Environment: The excretion of resistant enteric bacteria in animal waste likewise creates exposure pathways between food animals and human populations. Each year, according to USDA, confined food animals produce 335 million dry tons of waste, more than 40 times the mass of human biosolids generated by publicly owned treatment works (7.6 million dry tons were generated in 2005, for example).

When applied to farmland as fertilizer, typically without any pretreatment, animal waste contaminates surface and groundwater. Resistant *E. coli* and resistance genes have been detected in groundwater in North Carolina, Maryland, and Iowa (Anderson and Sobsey, 2006; Stine, et al., 2007; Mackie, et al., 2006). Resistant bacteria have also been isolated in air samples collected downwind of production facilities, while fewer bacteria were identified in samples collected upwind (Gibbs, et al., 2006).

Given the ability of bacteria to exchange resistance genes in the environment, and the numerous environmental pathways that connect food animal production with human populations, no method of controlling the spread of pathogens can substitute for ending the practices that have accelerated the development of antimicrobial resistance. Just one resistant bacterium that "escapes" can quickly reproduce, creating countless opportunities for human exposure.

Rural Communities: Rural communities and farmworkers face especially high risks of infection with antibiotic resistant bacteria and suffer disproportionately from the use of antimicrobial drugs in food animal production. Researchers have repeatedly documented this disproportionate risk (Van den Bogaard and Stobberingh 1999; Price, at al., 2007; Ojeniyi 1998; Saenz 2006; Smith, et al., 2005; and KE Smith, et al. 1999).

Policy Responses

There is consensus within public health and human medicine that the administration of antimicrobial drugs as growth promoters in food animal production should end. The American Public Health Association has called for banning non-therapeutic use of antimicrobials in food animal production (APHA, 2003). The World Health Organization, the American Medical Association, and the Infectious Diseases Society of America have made similar recommendations (WHO, 2003; Fryhofer, 2010; Spellberg, 2008).

The WHO has stated, "In the absence of a public health safety evaluation, [governments should] terminate or rapidly phase out the use of antimicrobials for growth promotion if

treatment options, increased health care costs, and heightened virulence of bacterial infections — more than offsets these supposed benefits. Nevertheless, producers and integrators ignore these health costs, which have been externalized to the larger society, and are not captured in the retail price of consumer meat products (Osterberg and Wallinga, 2004).

Conclusion

The Food & Drug Administration recently released a draft "guidance document" that reviewed the evidence linking antimicrobial resistance to food animal production. FDA concludes, "Using medically important antimicrobial drugs for production purposes is not in the interest of protecting and promoting public health" (FDA, 2010). FDA clearly supports the conclusions of public health researchers discussed here, and has begun taking action in response to antimicrobial resistance accelerated by animal agriculture. No *scientific* debate exists on these issues — only political questions remain.

I commend members for their leadership on this topic, and urge further action to fully prohibit using antimicrobial drugs for growth promotion and prophylaxis. Preserving the efficacy of antimicrobials in human medicine requires immediate action, and I urge Congress to move quickly in taking steps to protect the public's health.

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STATEMENT FOR THE RECORD
Subcommittee on Health, Committee on Energy & Commerce
U.S. House of Representatives
For the hearing, "Antibiotic Resistance and the Use of Antibiotics in Animal Agriculture"

July 14, 2010

Bill Kurtis,
Chairman and Founder
Tallgrass Beef Company (A grass-fed and grass-finished company)

The Grass-fed Alternative

If antibiotics were so important to raising beef, I often wonder how millions of cattle survived the cattle drives from Texas to Kansas and eventually to Chicago's stockyards in the 1800's. But they did survive, primarily on a diet of grass and forage as they have evolved over thousands of years.

Today, only a few ranchers in the United States raise cattle on grass, start to finish, compared with more than 90 million head that support a vast beef industry based on feeding *corn* to the animals. This change in diet occurred nearly sixty years ago and leads directly to our problems with feeding antibiotics to livestock.

Why the system changed can be traced to New Deal policies to save America's small farms during the Great Depression. Government price supports and direct subsidies made sure that corn, cotton, sugar, soybeans and wheat continued to feed us, even if all else failed.

Over the years, those farm policies would change but the subsidies, especially for corn, would never go away.

In addition, the agricultural colleges started experimenting with hybrid strains of agricultural crops to withstand changes in climate and fight pests. The result would increase yields, especially for corn.

And a third development would help revolutionize U.S. agriculture. A new fertilizer with ammonia nitrate could enhance the nitrogen content of soil to dramatically increase yields.

These three developments came together during WWII with amazing results. Without knowing it, the U.S. had created the ability to grow more corn than anywhere else in the world—and we did.

Corn was piled beside grain elevators and railroad tracks for lack of rail cars to transport it. Farmers sought new markets for corn preferring to sell it rather than bury it.

One alternative was to feed the corn to livestock. The starch and sugar created extra intramuscular fat that was promoted as "marbling". It made the meat juicy and tender and allowed the animals to fatten quickly.

By the early 1950's, large feeding operations began to concentrate thousands of animals into paddocks so they could be served by one feed truck. The diet was

Since *grass-fed* and *grass-finished* means no corn or grain is used as feed, there are no feedlots and hence, far fewer occasions to need antibiotics. My company, Tallgrass Beef, doesn't use any. No growth hormones are administered. The environment is better for it—the cattle graze the pastures and naturally fertilize it too, without producing an overabundance of waste in one concentrated location, as often occurs with feedlots.

The cattle are treated humanely.

The grass-fed movement is gaining momentum because the beef tastes richer, more like the original taste. And once the chemicals are removed, grass-fed beef, according to Clemson University researchers, contains twice the amount of a potent cancer fighting compound called conjugated linoleic acid. They found the beef is leaner and contains greater concentrations of desirable fatty acids and antioxidants. These benefits come from raising cattle without the use of any antibiotics.

Grass-fed beef will not replace the corn-fed model overnight but the potential benefits offer an intriguing alternative to the concentrated feeding operations and their need for antibiotics. Right now, it's a niche market in the scheme of things. But given a little help in the form of research and government incentives to expand the grass-fed, grass-finished program, I think it could provide valuable answers to the beef industry's problems.

bkurtis@tallgrassbeef.com

STATEMENT FOR THE RECORD
Subcommittee on Health, Committee on Energy & Commerce
U.S. House of Representatives
For the hearing, "Antibiotic Resistance and the Use of Antibiotics in Animal Agriculture"

July 14, 2010

Everly Macario, ScD, MS, MEd
Public Health Communications Research Consultant

As a public health communications professional working for the renowned MRSA Research Center at the University of Chicago, I am committed to protecting human lives and educating the medical community and general public about ways to prevent deadly antibiotic-resistant infections. Those of us working to promote public health greatly appreciate the Subcommittee on Health's recent attention to the growing public health threat of antibiotic resistance, including today's hearing specifically on the contribution of animal agriculture to the problem. I sincerely hope this interest does not fade before solutions are found and acted upon. I wish to submit this written testimony to express my strong support for the Preservation of Antibiotics for Medical Treatment Act (PAMTA, H.R. 1549, S. 619), a key component of any comprehensive set of solutions, which would institute a public health approach to antimicrobial use in food animals. I urge the Subcommittee to follow these hearings with prompt legislative action to pass PAMTA to greatly reduce the non-therapeutic use of important antibiotics in animal feed and water.

My interest in this issue is not purely professional, however. My beautiful curly reddish-haired cherub of a boy, Simon, is dead. As short and cold as that sentence feels, that is how it happened. Hearty and healthy at 1 ½ years of age, one random Friday morning six years ago, Simon woke not feeling well. By afternoon his face was cold and his breathing was labored. At nightfall he was bloated, covered in purple splotches and went into septic shock. He never woke up again. I need not delve into the feelings of desperate, painful insanity that I felt, and still feel, about this unfathomable experience. It is a parent's worst nightmare.

It is not possible for me to "wake up" from this nightmare. But we as a society must wake up and prevent other nightmares from occurring by preserving the efficacy of our antibiotics.

At the time of Simon's death, no one—really, no one, including the highly competent University of Chicago healthcare providers—knew why Simon had died. We learned only after an autopsy that Simon had contracted an antibiotic-resistant bacterium called, MRSA, or methicillin-resistant *Staphylococcus aureus*. And, it was the relatively new community-associated MRSA strain, not the more commonly known health care-associated strain. You're asking, "What is that?" That is what my husband and I (two PhD-level professionals, mine in public health) asked as well. My husband and I racked our brains endlessly wondering what we could have done to prevent Simon's death. To this day I do not know how Simon contracted this bug and why *he* was susceptible to it.

If someone had asked me, before Simon died, what I would do if I lost a child, I know that I would have responded something to the effect of not being able to go on with life. To my astonishment, people that I have met and would not have met if Simon had not died, such as other parents who lost children and a slew of health care and media folks, have somehow kept me afloat by validating my feeling that losing a child should not be allowed by the laws of nature. Others at the University of Chicago helped me focus on a bigger cause and made it possible to found a

Everly Macario's Story

An Excerpt from *Superbug: the Fatal Menace of MRSA*, by Maryn McKenna, copyright 2010, pages 53-56:

"They were children like Simon Sparrow, son of Everly Macario and James Sparrow, who woke with a shriek on April 16, 2004.

Macario and Sparrow had lived in Chicago for about eight months, brought there by Sparrow's new job as an assistant professor of history at the University of Chicago. It was a rare and precious tenure-track position at a school known for commitment to the liberal arts, so Macario, who had been teaching at Harvard, had been content to let her husband relocate them. Since the move at the start of the 2003 school year, she had been working from home as a consultant, a choice that let her raise seventeen-month-old Simon and his older sister Elena, who was four and a half. Macario's last degree had been a ScD, the PhD-equivalent conferred by the Harvard School of Public Health. Her specialty was public-health campaigns that persuaded people to use condoms and wear bike helmets and eat more vegetables.

'I thought we were done with infectious diseases,' she said ruefully. 'I thought what I was doing was what we needed to do next to improve our health.'

In April 2004, the couple had just filed their taxes and signed the papers for a Hyde Park condo. Sparrow's new job was going very well, and Everly had as much work as she wanted. 'Beautiful kids, dream jobs, a great neighborhood,' she said, looking back. 'We would hold each other and say, 'it's too good to be true.'

Simon was big for his age and sturdy except for a touch of asthma, with Macario's dark eyes and a mop of red-gold curls from his father. When he woke disoriented and feverish, they thought he might have a cold, or a return of a throat infection and breathing problems that he had been diagnosed with two weeks earlier. Macario had taken him to the emergency room for that and brought him home with a prescription for antibiotics and steroids. It was 7:30 a.m. and Elena had a stomach virus that Macario was already handling, so she let her husband take Simon to the ER this time. A few hours later, with Elena tucked in at home and being minded by their nanny Marcario met Sparrow at the hospital for a hand-off. He was due to drive to Peoria, three hours to the south, to give a speech. Simon was restless, squirming and wanting to be held but X-rays and all his test results were unremarkable. The ER staff sent Macario home with him.

On the way out of the ER, she noticed that his lips looked blue. At home, Elena was throwing up, and soon Simon was too, though he had not had anything all day but water. He rested on Macario's lap, and after an hour or so, she noticed that he was laboring to breathe, pushing out his chest and using the little muscles between his ribs

STATEMENT FOR THE RECORD
Subcommittee on Health, Committee on Energy & Commerce
U.S. House of Representatives
For the hearing, "Antibiotic Resistance and the Use of Antibiotics in Animal Agriculture"
July 14, 2010

Raymond J. Tarpley, D.V.M., Ph.D.

I am Raymond Tarpley, a veterinarian in College Station, TX, with an interest in acquainting veterinary students, veterinarians and biologists with the emerging field of Conservation Medicine, linking human, animal and environmental health. I am retired from the veterinary faculty at Texas A&M University where I taught anatomy, and I am currently enrolled in the MPH program at the Johns Hopkins Bloomberg School of Public Health.

I am writing to express my concern regarding the administration of low-dose antimicrobials to healthy animals for non-therapeutic uses in the animal production industry. Even as a veterinary student studying pharmacology many years ago, one of the bedrock concepts impressed upon me again and again was that if we as veterinarians chose to use an antibiotic, it was essential that it be administered in sufficiently high doses for a long enough period of time to avoid what was considered malpractice – the selection for resistant bacteria that could harm antibiotic efficacy. To this day, I cannot use an antimicrobial without this sacrosanct principle coming to mind.

U.S. industrial animal agriculture routinely incorporates low-dose concentrations of antimicrobials into the feed or water of healthy production animals to promote growth and feed efficiency, an application currently permitted by the U.S. Food and Drug Administration (FDA). It is widely recognized that this practice selects for bacterial resistance to these antibiotics, and there has been concern that such resistance could negatively impact public health.

Considerable evidence has accumulated that these resistant organisms (and/or antimicrobial residues) move beyond the food animal production environment via 1) food products, 2) soils (upon which animal wastes are applied), 3) water (waste runoff into surface streams and seepage into underground aquifers, 4) crops (antimicrobial uptake from soil), 5) air (blown out of animal confinement facilities by industrial fans), 6) insect carriage (e.g., flies), 7) rodent carriage and 8) human carriage (e.g., farm personnel).

During a time when bacterial resistance to an array of antimicrobials is increasing, renewed attention has been directed toward the threat that resistance arising from low-dose use of antimicrobials in food animals could pose for human and veterinary pharmaceuticals, particularly with fewer novel antimicrobials reaching the market. We now know that resistance to antimicrobials can develop rapidly, extend to other antimicrobials in the same or a different class, and be shared among bacteria through multiple genetic exchange mechanisms within or between genera, culminating in multi-drug resistance in some organisms.

While the FDA Center for Veterinary Medicine has acknowledged the threat of microbial resistance with their June 2010 draft guidance (#209) on the judicious use of antimicrobials in food animals, regulatory action has been slow to evolve on this problem, particularly in an atmosphere of industry pushback. Nonetheless, discontinued use of antimicrobials for non-

data from Scandinavian countries, including Denmark, Sweden, Finland and Norway, reveals that these disease spikes did not always occur, and when they did, could be controlled by evidence-based management protocols, while reducing antimicrobial resistance. With feed formulations that lowered protein content, strict sanitation protocols, more humane treatment of production animals and the use of antimicrobials by prescription as needed for sick animals, animal production did not suffer following the bans, nor was there increased mortality.

While fearing that animal health and welfare will be threatened by bans on low-dose antimicrobial use in feed and water, the AVMA nevertheless acknowledges that the Denmark data do "show that swine production, average annual number of piglets per sow, and weaned and finishing (just prior to slaughter) pig average daily weight gains have increased and weaned pig mortality (death rate) has drastically decreased in recent years". By encouraging industry toward more sophisticated, time-tested husbandry practices, combined with the use of antimicrobials as needed by veterinarians to treat sick animals, the animal production industry can operate efficiently while addressing root causes of disease and microbial resistance that will simultaneously eliminate the need for antimicrobials as growth promoters or as deterrents to subclinical disease, while reducing public health risks.

Currently there is a House bill, the Preservation of Antibiotics for Medical Treatment Act (PAMTA, H.R. 1549) that can begin to transition industry and veterinarians toward a more controlled use of antimicrobials as supported by the best science over the past 20 years. I believe this bill holds promise for the nation, and I strongly hope that all professionals in the health field will endorse it with enthusiasm. Since the first objective of medicine is to do no harm, this bill is reasonable in that it requires industry to prove the safety of its practices, rather than have the public first prove itself to be harmed.

Antimicrobials are critical for contemporary human and veterinary medicine, and all interventions should be considered that protect and conserve their value. If the use of low-dose antimicrobials for growth promotion can be safely discontinued by adopting improved strategies for disease prevention, not only will the expense of these antimicrobials be recovered by the producer, but the levels of resistant organisms escaping from the farm environment will be mitigated. By making antimicrobials available for farm use only through veterinary prescription, prudent and transparent application of these valuable pharmaceuticals will be better assured, while the reduction of resistant bacteria achieved by withdrawing their low-dose use will help preserve their efficacy.

STATEMENT FOR THE RECORD
Subcommittee on Health, Committee on Energy & Commerce
U.S. House of Representatives
For the hearing, "Antibiotic Resistance and the Use of Antibiotics in Animal Agriculture"

July 14, 2010

Patricia Whisnant, D.V.M.
American Grassfed Beef
Rain Crow Ranch
Doniphan, Missouri

Use of Antibiotics in Livestock Production

Has it only been a generation since antibiotics represented the world's first miracle drugs? Prior to their discovery death could occur in what would seem to be very trivial injuries and diseases. What have we allowed to happen to this powerful gift of healing? Today antibiotic-resistant bacteria have become a growing public health crisis that puts our health, our finances and even our lives at risk. MRSA, along with resistant strains of salmonella, campylobacter, and E.coli have heightened our awareness of the risk we have incurred in such a short time and alarmed us to a very real threat.

I recall the warnings of one of my professors in veterinary school that we, as veterinarians, were being given a sacred trust and responsibility in the use of these drugs and they should be used wisely. As he was reaching retirement age our professor told us how as a young man coming home from WWII he had contracted a lung disease caused by a bacterium similar to tuberculosis. They gave him little hope of survival but offered to try an experimental drug, an antibiotic. Doomed to life in a sanitarium and early death, he gratefully chose to take part in the experiment. He fully recovered due to the new miracle drug. His story and strong warning has always made me consider the judicial use of antibiotics. Even then, in the beginning of my career, we understood that the overuse of antibiotics was already creating "superbugs" resistant to medication. It has been estimated that at least 18,000 Americans die every year from drug-resistant infections. This does not take into account the increase in health care cost and human suffering associated with antibiotic-resistant bacteria.

Antibiotics probably single-handedly propelled my profession and that of human physicians into the respected world of science by the dramatic effects of their administration in diseased animals and humans. Their judicious and therapeutic use is still important for the health and recovery from disease of many. It is not the therapeutic use of antibiotics with which I have an issue. It is the non-

principles of animal husbandry that allows fulfilling the natural behavioral instincts of the animal in a clean natural environment allows for fewer pathogenic factors leading to disease and hence fewer drugs to treat disease. A pasture based system allows this to occur. In fact, that is how livestock was raised for thousands of years, right up until the mid-20th Century. It is not something new but rather a return to basics, raising animals how they were intended to be raised. The modern idea that the only way to feed the world is to raise animals in CAFO's using low dose antibiotics is just wrong. "Cheap food" but at what cost? I am not sure society is willing to pay the price to animal health, the environment and the effect on human health.

Today, many small, sustainable farmers do not use antibiotics at all, in large part because they don't have to compensate for unhealthy conditions and are not trying to unnaturally increase growth rate. On sustainable farms, animals are raised in a clean environment that promotes their health. Other sustainable farmers use antibiotics, but only to treat sick animals. The practice of feeding antibiotics to farm animals to promote faster growth is being phased out in countries around the world to protect the public's health. Given the lack of demonstrable benefits, the U.S. meat industry should heed the call of the U.S. public health community and global authorities to follow this lead.

The key to stopping non-therapeutic use of antibiotics as well as reducing the need for therapeutic doses is to consider agricultural models that promote wellness. What we need to do is encourage farming systems in which we are actively managing animals so they can develop strong natural immune systems – a concept sometimes called "positive health." We should not raise animals in an environment of stress that challenges the animal's capability to fight a pathogen without the use of low dose antibiotics.

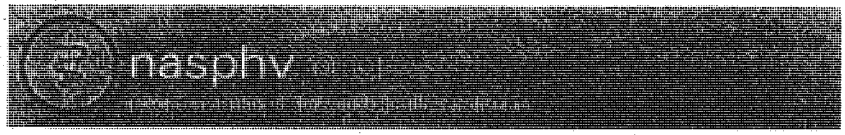
Research shows that animals that are under stress have reduced immunity. And, if animals are kept on farms where they are not overcrowded, where they have access to pasture and space to move around, where they are fed a diet that matches their natural needs, and where they are managed to promote health and well-being, then the levels of stress and the incidence of disease – and the need for antibiotics – is much, much lower. Speaking from my personal experience I cannot recall the last time I had to use therapeutic antibiotics on an animal from our farm. It is that simple.

The solution lies in looking at the causes of antibiotic-resistant infections – including intensive farming that relies on excessive amounts of low-dose antibiotics – and putting a stop to the continued non-therapeutic use of these vital medicines on which these farming systems are so dependent. Antibiotics themselves are not the problem. The irresponsible use of antibiotics is the problem. And, it's not the farmers that are at fault; it is the farming systems which result in the need for indiscriminate antibiotic use.



Council of State and Territorial Epidemiologists

Leaders in Applied Public Health Epidemiology



CSTE POSITION STATEMENT 1999-ID 7

COMMITTEE: Infectious Diseases

TITLE: Discontinuation of antimicrobials used to promote growth of food animals if they are used in or select for cross resistance to antimicrobials used in human therapy

ISSUE: Compelling scientific evidence indicates that use of antimicrobials in food animals results in antimicrobial resistance which can be transmitted to humans through the food supply and lead to adverse health consequences. An area of particular public health concern has been the feeding of antimicrobials in subtherapeutic doses to animals to promote growth. The World Health Organization recommends that antimicrobials not be used as growth promotants if they are used for or select for cross-resistance to antimicrobials used in human medicine. Discontinuing the subtherapeutic uses of these antimicrobials in food animals is needed in the United States as part of a comprehensive plan to reduce antimicrobial usage and ultimately protect the public health.

POSITION TO BE ADOPTED:

CSTE and NASPHV recommends the discontinuation of antimicrobials used to promote the growth of food animals if they are also used in human medicine. These uses may increase antimicrobial resistance and no longer meet the food safety criteria of reasonable certainty of no harm.

BACKGROUND AND JUSTIFICATION:

Antimicrobials are used for the treatment of sick animals, the prevention of selected animal production diseases. Subtherapeutic use of antimicrobials provide an economic advantage to the producer by decreasing the amount of feed needed. However, these antimicrobials are not essential for food production animals to reach their full genetic potential. The World Health Organization (WHO) recommends that antimicrobials not be used as growth promotants if they are used in or select for cross-resistance to antimicrobials used in human medicine. Consistent with the WHO recommendations, the European Union prohibited the use of the four such antimicrobials used in humans which were still used as growth promotants in Europe (virginiamycin, bacitracin, tylosin, and spiramycin).

For example, there is evidence that use of avoparcin, a glycopeptide, to promote growth of food animals in Europe resulted in a large reservoir of vancomycin-resistant enterococci (VRE) in food animals, which were transferred to humans through meat and poultry, resulting in carriage in humans. The public health concern is that these colonized humans could introduce VRE to hospitals. Because of documented community carriage of vancomycin resistant enterococci in humans and the importance of vancomycin as a therapeutic agent to treat hospital acquired enterococci infections, the European Union banned avoparcin use in food animals. Following

the ban on avoparcin use, there was a decline in prevalence of VRE in food animals, meat and poultry, and humans in Europe.

In the United States, seven of 17 FDA licensed antimicrobials currently used subtherapeutically in food animals to promote growth or enhance feed efficiency are also used in or select for cross-resistance to antimicrobials in human therapy. These are bacitracin, lincomycin (selects for cross-resistance to clindamycin), oxytetracycline, penicillin, tetracycline, tylosin (selects for cross-resistance to erythromycin), and virginiamycin (selects for cross-resistance to quinupristin/dalfopristin). The subtherapeutic use of virginiamycin to promote growth in food animals in the United States threatens the effectiveness of quinopristin/dalfopristin (Synercid), which will soon be approved in the United States for the treatment of multidrug-resistant VRE; such isolates are often resistant to all other available antimicrobials. Virginiamycin, which is only used at subtherapeutic levels, has resulted in a reservoir of Synercid-resistant E. faecium in food animals. A preliminary survey of retail chicken products by CDC and four state health departments has found Synercid-resistant E. faecium in over half of the culture-positive chickens. Furthermore, preliminary data indicates that between 1-2% of persons in the general community may be carrying Synercid-resistant E. faecium. It appears likely that the use of virginiamycin to promote growth in food animals has resulted in Synercid-resistant E. faecium which is of concern because Synercid will likely be the drug of choice to treat multi-drug resistant VRE in infected patients.

The US Food and Drug Administration is responsible for ensuring the food safety criteria of a "reasonable certainty of no harm" with all approved antimicrobial uses in food animals. There is sufficient scientific evidence that subtherapeutic use of antimicrobials in food animals can select for antimicrobial resistance and do not meet this food safety criteria. In December 1998, US Food and Drug Administration proposed a new framework for evaluation of antimicrobials used in food animals. Although the proposed framework may be used to evaluate the existing approvals for subtherapeutic uses of antimicrobials in food animals, the details of how the proposal would be implemented remain to be determined, making it unlikely that the subtherapeutic use of these antimicrobials would be addressed for several years. More timely action is necessary to protect the public health. Antimicrobials which are used in human medicine, or which select for resistance to antimicrobials which are used in human medicine, should not be used to promote the growth of food animals.

July 12, 2010

To the House Energy and Commerce Health Subcommittee:

When the American Medical Association, American Academy of Pediatrics, World Health Organization, and American Public Health Association all agree on a health care policy issue it's worth taking notice. Each of these leading organizations has forcefully urged an end to the rampant overuse of antibiotics in the poultry and livestock industries. Why? Because an estimated 70 percent of the antibiotics used in the United States are fed to animals that are not even sick, making germs drug resistant, and jeopardizing the ability to effectively treat serious diseases in both humans and animals.

When antibiotics were introduced in the 1940s and 1950s they were celebrated as revolutionary. Indeed, many heralded them as ending the terrifying era when disease plagues swept through nations. In 1969, the Surgeon General, in a message to Congress, stated "It is time to close the book on infectious diseases. The war against pestilence is over."

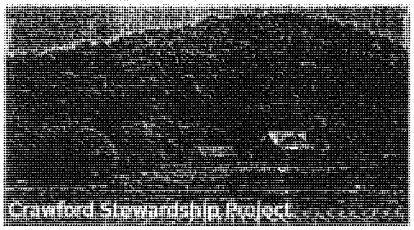
But no one is saying that these days. With each passing year, research indicates that many common infectious diseases are developing new and more problematic resistance to many common antibiotics. The Infectious Diseases Society of America now estimates that 90,000 people die every year of hospital-acquired infectious disease and that 70 percent have infections that are resistant to at least one antibiotic drug. Antibiotic resistant infections are estimated to cost the United States health care system as much as $26 billion annually, according to a Cook County, Illinois hospital study.

Using these drugs in livestock feed and water at low levels (subtherapeutically) is an especially foolhardy practice. It suppresses only the weak germs while allowing the strongest to live and multiply. Yet this is precisely the way most antibiotics are used at industrial animal operations. Rather than a therapeutic dose that would kill all of the illness-causing germs, the drugs are added at lower levels to daily feed or water of chickens, turkeys, pigs and other food animals. This is done both to stave off disease in crowded, unsanitary conditions, and to trigger faster growth.

But this common practice puts the public at risk. Food animals shed resistant bacteria in their feces, breath, and in their skin. Research by the Department of Agriculture and Johns Hopkins School of Public Health has shown that manure contaminated with resistant pathogens can migrate around a farm, in slaughter and meat processing (thus contaminating food), into neighboring farms and the environment, and even travel long distances in the air.

After a two and half year process of research and deliberation, the Pew Commission on Industrial Farm Animal Production (of which Bill was a member) concluded that curbing non-therapeutic antibiotic use at industrial animal farms was essential to protecting public health. The Commission's Chair, former Kansas governor John Carlin, recently stated, "More than three decades of research have shown that overuse of antibiotics in food-animal production contributes to antibiotic resistance in humans."

Crawford Stewardship Project



Crawford Stewardship Project
PO Box 284
Gays Mills, WI 54631

crawfordstewardshipproject.org
csp.county@gmail.com
608-735-4277

July 8, 2010

RE: the use of human Antibiotics in farming

I am writing on behalf of the 680 supporters of Crawford Stewardship Project. As advocates for farm families in Western Wisconsin, we are highly concerned about the current us of human antibiotics in agriculture.

It is estimated that up to 70 percent of all antibiotics sold in the U.S. are given to healthy food animals. As doctors have always warned, administering low doses of antibiotics over long periods of time is exactly the wrong way to treat these life saving drugs, but that is precisely what is happening. On many industrial farms across our nation, human antibiotics are being administered to healthy animals in low dosages over long periods of time, not to treat any illness whatsoever.

Taking action on the use of human antibiotics industrial farms would benefit Wisconsin in the following ways. First, by protecting people from potential life threatening diseases that are born on industrial farms. Second, by upholding the efficacy of antibiotics for patient use, especially when a life is on the line, or in elderly folks. The AMA and many medical groups support a change because it is doctors that depend daily on these live saving drugs to do their jobs. And lastly, by helping to encourage and improve our agricultural system. Wisconsin is home to tens of thousands of family farms who use antibiotics wisely, they let their cows out to pasture, and they actually care about the lives of each animal on the farm. Upholding those values is important, and at the same time we need to send a message to industrial farms that they should consider a more ethical way to raise and take care of



Wisconsin Association of School Nurses

July 12, 2010

Honorable Congresswoman Tammy Baldwin
2446 Rayburn Building
Washington DC 20515

Dear Rep. Baldwin,

The Wisconsin Association of School Nurses supports the belief that the use of antibiotics in agriculture should be therapeutic only – and that non-therapeutic use should be prohibited. Human antibiotics are far too critical to human life to simply be used preventatively or to encourage growth in food animals. Other countries have proven that farming can be done without the use of non-therapeutic antibiotics, and the Wisconsin Association of School Nurses strongly encourages Congress to pass similar measures.

While we believe that limited antibiotic use to treat sick animals is necessary and advisable, the consequences of antibiotics misuse are unjustified.

WASN supports this change because the current practice undermines the medical treatment of significant and often life-threatening infections. This change will be best for all people, for animals and especially for those who need antibiotics to be effective because their lives depend upon it.

Please consider taking action on this issue – and accept our thanks for your service and work.

Sincerely,

Ann Riojas, President
Wisconsin Association of School Nurses
riojasak@milwaukee.k12.wi.us

WISCONSIN
FARMERS UNION

July 9, 2010

Honorable Congresswoman Tammy Baldwin
2446 Rayburn Building
Washington DC 20515

Regarding: Non-therapeutic antibiotics use in farming

Dear Rep. Baldwin,
The Wisconsin Farmers Union represents thousands of farms across the state of Wisconsin – and has been closely following the issue of antibiotic use in agriculture.

The Wisconsin Farmers Union policy on antibiotic use on farms is:

> Most antibiotics in animal husbandry are used for the prevention of sickness and to accelerate growth. In order to ensure human health and consumer confidence, WFU supports policies that require independent monitoring of data on the use of antibiotics at food and feed companies, encourage USDA to increase testing for pathogens in processing plants, limit the use of antibiotics to the treatment of disease in livestock and not to compensate for inadequate animal husbandry, environment or genetics.

We believe that the use of antibiotics in agriculture should only be therapeutic. Human antibiotics are far too critical to human life to simply be used preventatively or to encourage growth in food animals. Other countries have proven that farming can be done without the use of non-therapeutic antibiotics, and the Wisconsin Farmers Union encourages Congress to pass similar measures.

While we believe limited antibiotic use to treat sick animals is necessary and advisable, the consequences of antibiotics misuse is wholly unjustified. Please consider taking action on this issue – and accept our thanks for your service and work.

Sincerely,

Scott Schultz
Executive Director

117 West Spring Street • Chippewa Falls, WI 54729 • Ph: 715-723-5561 or 800-272-5531 • Fax: 715-723-7011
www.wisconsinfarmersunion.com • info@wisconsinfarmersunion.com

Testimony for the record
Congressman Leonard L. Boswell
Before the House Committee on Energy and Commerce, Health Subcommittee
Hearing on antibiotics resistance and the use of antibiotics in animal agriculture
July 14, 2010
2 p.m.

Chairman Pallone, Ranking Member Shimkus and members of the Health Subcommittee, I would like to thank you for allowing me the opportunity to submit my testimony for the record today. I have spent most of my life involved in animal agriculture and have seen first-hand the responsible use of antibiotics.

I understand the issues that affect the livestock, dairy and poultry industries having spent most of my youth working in livestock production, and I still have a hand in managing a cow-calf operation on my farm in Lamoni, Iowa today. After I retired from 20 years in the Army, I moved back to Iowa to begin farming. Part of my preparation included a consultation with my local veterinarian to discuss the use of antibiotics to treat sick animals and prevent future illness. From my experience with producers and veterinarians, the thoughtful use of antibiotics is not the exception, it's the rule.

During the 110th Congress, it was my privilege to serve as Chairman of the Agriculture Subcommittee on Livestock, Dairy and Poultry. On September 25th of last year, we held a hearing to review the advances in animal health within the livestock industry. We were specifically looking at how antibiotics are used on America's livestock farms. Our witnesses included veterinarians from USDA's Animal Health and Plant Inspection Service and FDA's Center for Veterinary Medicine (CVM), producers, veterinary practitioners and academics from across the country. I believe that we heard from a good cross-section of the users of the animal health products, the doctors responsible for the use of antibiotics, and the experts studying the resistance trends from use of antibiotics in animals.

As the Subcommittee members listened to the witnesses, it became very clear that America's livestock, dairy and poultry producers have a responsibility to safeguard animal and public health. This is a responsibility they take very seriously. They are committed to using antibiotics responsibly and have developed responsible-use guidelines for each of their respective industries. They didn't develop these guidelines because Congress told them to do so;

they developed the guidelines because it was the right thing to do for their animals and their consumers.

Much has been discussed about the Denmark antibiotic ban. However, I believe that experience has been often mischaracterized.

In the mid-1990's the European Union made a decision to phase out the use of antibiotics as growth promoters. Denmark, which had a pork industry roughly equivalent to the size of the pork herd in Iowa (which is the largest pork producing state in the country), instituted a full, voluntary ban in 1998 which became mandatory in 2000. Many proponents of restricting the use of certain animal antibiotics as a model often point to this ban instituted in Denmark, citing a drop in total tons of antibiotics used in pork production in that country. Interestingly, what the proponents never seem to discuss are the other effects of that ban. After the ban became fully implemented in 1999, Danish pork producers saw an immediate increase in post-weaning diarrhea and an increase in piglet mortality, which has had long-lasting effects on the Danish pig industry. The increase in piglet deaths and the overall impact on animal well-being might be acceptable if it resulted in improvements to public health, but such improvements have not materialized. And while overall use of antibiotics in Denmark declined, there has been a marked increase in the therapeutic use of antibiotics – those used to treat and control diseases. Today, the use of therapeutic antibiotics in Danish pigs now surpasses what was used to prevent disease and promote growth prior to the ban in 1999 and continues to rise each year.

I had the opportunity to travel to Denmark in September 2009. During that trip I met with a large cross-section of the Denmark livestock industry. I found out that because of the ban they have lost over 80 percent of their producers - going from approximately 28,000 to 5,000 - and pork processors went from 67 to two. In my experience, less food production capacity is a greater threat to food security.

Also, during that trip I had the opportunity to meet with several farmers. During informal conversations one producer stated that they thought the United States should implement a similar ban as well because it would make them more competitive. We must ask ourselves why we are pushing for this ban. Is it to reduce antimicrobial resistance of humans? There has been no decisive scientific data to support this to date. Is it to make Denmark more competitive with U.S. livestock producers? I certainly hope not.

A ban similar to Denmark's will also have a huge impact on the cost to produce meat products. A 2009 Iowa State University study estimated that the effect of a ban in the United States similar to Denmark's would raise the cost of production by $6 per pig in the first year after such a prohibition; 10 years after the ban, the cumulative cost to the U.S. pork industry would exceed $1 billion.

A recent study by Dr. Scott Hurd, associate professor at Iowa State University's College of Veterinary Medicine and former U.S. Department of Agriculture Deputy Under Secretary for Food Safety, demonstrated that when pigs have been sick during their life, those pigs will have a greater presence of food-safety pathogens on their carcasses. This is a serious implication that must be considered when looking at the costs and benefits of antibiotic use in livestock.

Protecting human health and providing safe food are paramount concerns of America's livestock producers.

If policy decisions are going to be made regarding antibiotic use, we must ensure that we are using all of the science out there and not just looking at Denmark through a limited lens.

Again I would like to thank you for allowing me the opportunity to submit my testimony for the record. I hope as a farmer and user of antibiotics I have offered you some insight into the livestock industry's perspective. In the United States we are very blessed to have the safest, most plentiful, and most affordable food supply in the world. As policymakers we must take a hard look at how our decisions affect human health and our ability to feed ourselves and the world.

Thank you.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

The Honorable Henry A. Waxman
Chairman
Committee on Energy and Commerce
House of Representatives
Washington, D.C. 20515-6115

NOV 03 2010

Dear Mr. Chairman:

Thank you for providing an opportunity for the Food and Drug Administration (FDA or the Agency) to testify at the July 14, 2010, hearing before the Subcommittee on Health, which examined antibiotic resistance and the use of antibiotics in animal agriculture. This letter provides responses to questions for the record, forwarded in your letter of August 10, 2010.

In the enclosed document, we have restated each question in bold type, followed by FDA's responses.

Thank you again for the opportunity to appear before the Subcommittee. We look forward to continuing to work with you on these important public health issues. If you have any further questions or concerns, please let us know.

Sincerely,

Jeanne Ireland
Assistant Commissioner
for Legislation

Enclosure

The Honorable Jan Schakowsky

1. **Doctor Sharfstein, you cite significant medical literature in your proposed guidelines stating the link between over-use and antibiotic resistance, yet the FDA's voluntary guidelines only address non-therapeutic use. I've heard that poultry farmers have recently stated that, from egg to slaughter, chickens and turkeys ALWAYS need antibiotics to prevent disease. How do you justify only addressing non-therapeutic use, and what is to prevent farms from re-categorizing the purpose of the antibiotics they give to animals, instead of actually ending over-use?**

FDA has focused on non-therapeutic uses (e.g., uses intended to enhance growth or improve feed efficiency) because we believe such uses are of greatest concern. Drugs used for this purpose: 1) are not being used to address any specifically identified animal health concern, 2) are typically being administered to herds or flocks of animals continuously in their feed, and 3) are being administered without any involvement of a veterinarian (i.e., they are currently marketed as over-the-counter products). However, some of the same drugs that are approved for such production (non-therapeutic) purposes are also approved for therapeutic purposes as well. In contrast to the production uses, these therapeutic uses are directed at specifically identified diseases and are administered in a more targeted way to certain animals for limited durations.

We acknowledge the importance of maintaining the availability of antimicrobial drugs for therapeutic purposes in food-producing animals. Although we do not agree with the statement that poultry need antibiotics on a continuous basis from egg to slaughter, we acknowledge the need to administer antibiotics to poultry or other food-producing animals to address animal health issues (i.e., to treat, control, or prevent specific diseases) As discussed in Draft Guidance #209 (*http://www.fda.gov/downloads/AnimalVeterinary/GuidanceCompliance Enforcement/GuidanceforIndustry/UCM216936.pdf*), FDA believes that certain preventive uses of medically important antimicrobial drugs are necessary and judicious.

The draft guidance provides some criteria for preventive uses to be considered necessary and judicious. When determining the appropriateness of a preventive use, important factors such as: 1) evidence of effectiveness, 2) evidence that such a preventive use is consistent with accepted veterinary practice, 3) evidence that the use is linked to a specific etiologic agent, 4) evidence that the use is appropriately targeted, and 5) evidence that no reasonable alternatives for intervention exist, should be considered.

As described in the draft guidance, FDA is recommending that medically important drugs be limited to uses in food-producing animals that: 1) are necessary for ensuring animal health, and 2) involve veterinary oversight or consultation. The implementation of these recommendations would practically mean that products currently marketed for production (non-therapeutic) uses would no longer be labeled and marketed for that purpose, and such products could now be dispensed only under the order of a veterinarian

We believe requiring such veterinary involvement is a significant factor in mitigating the concern that farms would simply "re-categorize the purpose of the antibiotics."

An additional deterrent to such re-categorization is the fact that current law does not permit the extra-label use of drugs in feeds. Therefore, once relabeled, producers and veterinarians would be required by law to use the drugs only for the labeled therapeutic uses.

2. Doctor Sharfstein, the FDA's new Guidance Document identifies certain uses of antimicrobials as creating a public health risk.

a. Why did you opt for voluntary guidelines as opposed to regulatory options that offer real enforcement?

The draft guidance is a document that frames FDA's thinking as we move forward. FDA is keeping all options on the table for addressing this issue. We think it is important to pursue all available pathways for implementing the principles outlined in Guidance 209, including working collaboratively with the animal pharmaceutical industry and exploring other options, such as potential regulatory action.

b. Since no regulatory action has yet been announced, should we assume you are focusing on voluntary approaches first? If so how long are you going to give this approach?

We are supportive of voluntary actions to address antimicrobial resistance. FDA has been actively seeking input from all of its stakeholders on approaches for addressing this issue and is encouraged that opportunities exist to make significant progress forward through the guidance process.

c. Does the FDA believe that drug manufacturers and farmers will voluntarily make changes that go against their financial interest?

FDA's Center for Veterinary Medicine has been actively reaching out to all stakeholders on this issue, including drug manufacturers, producers, and veterinarians. With regard to the animal pharmaceutical industry in particular, we are encouraged by the reaction of the Animal Health Institute that "welcomed" the recent publication of our draft guidance. We are also encouraged by the engagement of the animal pharmaceutical industry to date in substantive discussions on approaches for implementing FDA's recommendations.

3. In July 2008, the FDA proposed banning in the fall of 2008 the extra-label use of all cephalosporin antibiotics in food producing animals. In November 2008, the FDA said it would not implement the ban and would review the public

comments it had received on its July 2008 proposal. Dr. Sharfstein, you indicated in a letter dated December 16, 2009, that "FDA shares your concerns about the public health risks associated with the development of resistance to important antimicrobial drugs such as the cephalosporins. As the agency has indicated previously, we intend to issue another order of prohibition addressing the extra-label use of the cephalosporin class of drugs. The Center for Veterinary Medicine has completed its analysis of the public comments and has prepared a revised order. This document is currently undergoing review." Could you please indicate the status of the review and when the draft prohibition order can be expected?

This issue remains a priority for the Agency. While we cannot provide a specific timeline for publication, we are targeting the end of 2010 for completion of the revised order. We believe this is an achievable goal for an Agency draft prohibition order.

The Honorable John Shimkus

1. **Have all antibiotics available for livestock production been approved by FDA as safe and effective? Have they been subjected to safety testing for resistance in the past?**

The medically important antimicrobial drugs that are currently used for production purposes in animal feed (i.e., to promote growth, improve feed efficiency) were approved by FDA as safe and effective prior to the late 1970's. These drug products have not been subjected to the safety assessment process implemented through guidance in 2003 for evaluating antimicrobial resistance concerns.

2. **How do you determine when action should be taken for the protection of public health? What is the threshold? How do you respond to criticism that it is not a transparent process?**

FDA considers an antimicrobial new animal drug to be "safe" if the Agency concludes that there is "reasonable certainty of no harm to human health" from the proposed use of the drug in food-producing animals. This standard applies to safety evaluations completed prior to new animal drug approvals, as well as to those completed for drugs after approval. If this safety standard is not met before approval, the drug cannot be approved. If safety issues arise after approval, the Federal Food, Drug, and Cosmetic Act (FD&C Act or the Act) provides grounds for withdrawal of approval of new animal drug applications for safety reasons. Although the Agency is actively seeking to improve the transparency of all of its activities, certain limitations remain regarding disclosure of

certain information in cases where regulatory action is being contemplated for individual drug applications, especially when such action results in a formal evidentiary hearing.

However, FDA decided to first pursue solutions for addressing the public health concerns regarding antimicrobial use in animal agriculture through the issuance of Draft Guidance #209. We believe this provides for a transparent process of seeking input from all the affected stakeholders and the general public on strategies for addressing the issue.

The Agency has identified in the draft guidance its concerns that certain uses of medically important drugs are not judicious and are not in the interest of public health. Although we have not yet concluded that such uses are "unsafe" in the context of the Act, we believe there is sufficient scientific evidence to support the need for steps to address the public health concerns. The Agency requested public comment on the draft guidance. Though the docket formally closed on August 30, 2010, the public may submit comments on any FDA guidance document at any time. Regarding Draft Guidance #209, FDA received hundreds of substantive comments during the formal comment period and we are currently reading and considering each one. After this review is completed, the Agency will publish a final version of the guidance which may or may not include changes, depending on what new information has been provided in the comments. Only after finalization will Draft Guidance #209 become the Agency's formal policy on the judicious use of antimicrobial drugs in food-producing animals.

cc: The Honorable Frank Pallone, Jr.
Chairman
Subcommittee on Health
Committee on Energy and Commerce

The Honorable John Shimkus
Ranking Member
Subcommittee on Health
Committee on Energy and Commerce

The Honorable Joe Barton
Ranking Member
Committee on Energy and Commerce

QUESTIONS FOR THE RECORD
Deputy Administrator Dr. John Clifford, D.V.M.
Animal and Plant Health Inspection Service
U.S. Department of Agriculture

For the Committee on Energy and Commerce
Subcommittee on Health
U.S. House of Representatives
Hearing on Antibiotic Use in Animal Agriculture
July 14, 2010

Questions Submitted by the Honorable John Shimkus:

1. The term "growth promotion" seems to cause concern among some members of Congress. Is it true that the mechanism by which subtherapeutic antibiotics work to promote growth is by preventing diseases which would otherwise inhibit growth?

Antibiotics are used in animal agriculture for disease prevention, growth promotion, and treatment of diseased animals, but there is not a distinct boundary between which antibiotics have only growth-promotion effects without potential for therapeutic benefit. The mechanism of action for the growth-promotion effects of antibiotics is not well understood. A number of hypotheses have been proposed, but there is no recognized single explanation for the growth-promoting mechanism of antibiotics. Suppression of disease-causing pathogens, which can lead to improved animal health and welfare, is one recognized benefit of antibiotic growth promoters. Producers could also see benefits from the subtherapeutic use of antibiotics through improvements in feed conversion rates, which would help animals get maximum benefit from feed.

2. If legislation or regulation were enacted to ban the preventative uses of antibiotics, what does USDA calculate the cost to be for livestock producers? If USDA has not done this very basic cost analysis, why is your agency already supporting FDA's efforts to pressure livestock producers and animal health companies to eliminate these uses?

USDA has not calculated the economic impact on livestock producers because we are not requiring or mandating any specific actions on the part of producers.

USDA did consult with the Food and Drug Administration on its guidance document and supports its general conclusion that medically important antibiotics in food-processing animals should be used judiciously.

3. In follow-up to your testimony before the Subcommittee on Health, an e-mail was sent from USDA stating that "USDA does not support the broad elimination of antimicrobials for specific uses in animal agriculture." Since this is exactly what Representative Slaughter's legislation, H.R. 1549, attempts to do, can we infer from this statement that USDA opposes this legislation?

USDA does not support the broad elimination of antimicrobials for specific uses in animal agriculture. As we said in our testimony, determinations about the use of antimicrobials in animal agriculture must be

based on sound scientific evaluation and data-based decision making, to include the effect of changes upon animal health.

We believe that the current risk assessment process for antimicrobials, which the Food and Drug Administration has in place, can provide a scientific basis for decisions about specific antimicrobial use. This is preferable to a broad approach that eliminates whole categories of antimicrobials that may or may not have an effect on resistance.

With respect to your question on H.R. 1549, USDA does not have a formal position on the legislation.

4. With respect to FDA's proposed guidance for antibiotic use, Guidance 209, FDA has proposed to require veterinary oversight for certain uses of antibiotics in animals. How does USDA suggest producers in veterinary shortage areas comply with this guidance?

To clarify, the FDA guidance does not require veterinary oversight. The guidance is intended as a framework or suggestion to producers and veterinarians on the antimicrobial issue. There is no requirement that farmers or producers follow these guidelines, nor is there any sort of formal or informal enforcement mechanism related to it. The introduction to the guidance makes this clear when it says, "It does not create or confer any rights for or on any person and does not operate to bind FDA or the public."

Although there is no requirement that producers follow the guidance, we remain committed to working with all our Federal partners to address the concerns you have raised regarding veterinary shortages. We are especially concerned with the lack of large animal veterinarians in rural areas and the challenges that longer distances and traveling times for veterinary consultation pose. USDA believes that we must work with our Federal partners, veterinarians, and other stakeholders to find feasible solutions on this issue.

5. As you know, animals get sick just like people so should we not support the livestock industry's efforts to focus on the prevention of disease, not just trying to treat illnesses after they occur?

USDA believes that antimicrobials should be available for the treatment, prevention, and control of disease. Ultimately, the decisions on judicious antimicrobial use should be addressed through science-based risk assessment and evaluation. We believe that this standard should apply to their use in both human and animal populations. Above all, we believe that the judicious use of antimicrobials should not result in undue risk to human or animal populations.

HENRY A. WAXMAN, CALIFORNIA
CHAIRMAN

JOE BARTON, TEXAS
RANKING MEMBER

ONE HUNDRED ELEVENTH CONGRESS

Congress of the United States
House of Representatives
COMMITTEE ON ENERGY AND COMMERCE
2125 RAYBURN HOUSE OFFICE BUILDING
WASHINGTON, DC 20515–6115

Majority (202) 225–2927
Minority (202) 225–3641

August 10, 2010

RADM Ali S. Khan, M.D., M.P.H.
Assistant Surgeon General
Acting Deputy Director
National Center for Emerging and Zoonotic Infectious Disease (Proposed)
Centers for Disease Control and Prevention
1600 Clifton Road
Atlanta, FA 30333

Dear Dr. Kahn:

Thank you for appearing before the Subcommittee on Health on July 14, 2010, at the hearing entitled "Antibiotic Resistance and the Use of Antibiotics in Animal Agriculture."

Pursuant to the Committee's Rules, attached are written questions for the record directed to you from certain Members of the Committee. In preparing your answers, please address your response to the Member who submitted the questions.

Please provide your responses by August 24, 2010, to Earley Green, Chief Clerk, via e-mail to Earley.Green@mail.house.gov. Please contact Earley Green or Jennifer Berenholz at (202) 225-2927 if you have any questions.

Sincerely,

Henry A. Waxman
Chairman

Attachment

The Honorable John Shimkus

Q 1: In investigating cases of MRSA, what has CDC concluded about animal contact as a risk factor for these infections?

A. Methicillin-resistant *Staphylococcus aureus* (MRSA) ST398 is the predominant strain of MRSA identified in food-producing animals (primarily pigs) in Europe, Canada and the United States. Transmission of MRSA from either companion or food-producing animals to humans is thought to result from direct (i.e., skin to skin) contact and appears to account for an extremely small proportion of human MRSA infections in the United States.

Q 2: Is MRSA a foodborne infection, acquired by eating meat? If not, what is the pathway for resistance to be transmitted to humans?

A. Unlike antimicrobial resistant *Salmonella* and *Campylobacter* in humans, neither transmission of MRSA from contaminated meat or other food, nor an association with antibiotic use in animals, has been described. In community settings, most MRSA infections are acquired by direct contact with the infected skin of other humans or direct contact with objects that have been contaminated with wound drainage. In healthcare settings, MRSA is most often transmitted from patient to patient on the hands of healthcare workers that have not performed adequate hand washing.

In the United States, there have been no human infections to date identified with MRSA ST398 (the predominant MRSA strain identified in food-producing animals in Europe, Canada, and the United States). CDC analyzed its collection of over 10,000 MRSA isolates from human infections and human nasal swabs and did not find any MRSA ST398. A recent non-CDC publication identified nasal colonization (i.e., carriage without infection) with the MRSA ST398 strain in workers at one Midwestern swine production system; however, these persons did not have MRSA infections.[1]

CDC will continue to assess the implications for human health of MRSA in food and food-producing animals.

Q 3: Do you recognize any limitations in the charts you presented at the hearing, and should decisions be made based upon those charts with such significant limitations?

A: CDC presented antimicrobial resistance data associated with fluoroquinolone use in the United States, quinolone use in the United Kingdom, and ceftiofur use in Canada. During the hearing, there was concern voiced with the data presented from the United Kingdom because the data were considered dated. The purpose of presenting these data was to demonstrate clear examples on how antimicrobial use in animals results in resistance, both in animals and humans, following a new intervention. Please be assured that CDC makes decisions and

---

[1] Smith TC, Male MJ, Harper AL, Kroeger JS, Tinkler GP, et al. 2009 Methicillin-Resistant Staphylococcus aureus (MRSA) Strain ST398 Is Present in Midwestern U.S. Swine and Swine Workers. PLoS ONE 4(1): e4258. doi:10.1371/journal.pone.0004258
http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0004258

recommendations based on all the data available, including the more recent data presented from the United States; it presented the United Kingdom data as an example of resistance development rather than as the sole case upon which current recommendations are being made.

Ministry of Food, Agriculture and Fisheries
Danish Veterinary and Food Administration

23 August 2010

Replies to the Honourable John Shimkus on the Danish restrictions of non-therapeutical use of antibiotics for growth promotion and its consequences

1. Would you agree that weaning pigs, the most susceptible population, suffered most from the ban on growth promoters?

2. How do you account for the significant increase in therapeutic antimicrobials in swine between 1999 and 2000? And the continued high level use of therapeutics after that?

3. If you took an average of the 5-10 years before the ban and the 5-10 years after the ban, do you think you would find the same results others have – that therapeutic use has nearly doubled?

4. What kind of improvements have you seen in antibiotic resistance in humans since the ban?

5. Has the number of swine farms in Denmark increased or decreased since the ban? Have production practices intensified to compensate for the declining number of farms?

6. What has happened to total livestock consumption of all antimicrobials of human importance since 2000?

Replies:

1. As no other species or age group of animals were influenced by the ban it would not be correct to state that weaner pigs suffered the most. There was a slight increase of therapeutic antimicrobials for weaner pigs just after the ban which might be correlated to the ban, but this increase could also be correlated to disease outbreaks related to Lawsonia intercellularis in Danish swine herds. Regardless of the reason for the temporary problems in weaner production, this was solved, as the farmers continuously improved their management when producing weaners. Neither weaner mortality nor average daily weight gain was affected by the ban in the long run, but only temporary shortly after the ban (Aarestrup et al., AJVR, Vol 71, No. 7, July 2010).

2. The increase from 1999 to 2000 could be attributable to the temporary problems in weaner production after the ban or due to disease problems related to Lawsonia intercellularis. There has been a 50% reduction in the amount of antibiotics pr. kg. pig from 1994 to 2008. In 1994 the amount used was 99 mg and in 2008 this was 49 mg. Denmark has a very low level use of therapeutical antimicrobials compared to other countries with comparable pig production.

3. Therapeutic use has not doubled regardless of which years you compare before and after the ban. If others have found that, they probably have forgotten to take the increase in pig production by more than 25 % into account since the ban. As stated above there has been a 50% reduction in antimicrobials given pr kg pig.

4. Denmark has, compared to many other countries, traditionally had a low frequency of resistance among bacteria causing human infections. The ban on non therapeutic use of antimicrobial agents in Denmark was implemented to reduce an observed reservoir of bacteria in food animals and food products, which very resistant to classes of antimicrobial agents which at that time still had a limited use in human medicine.

   In connection to the different bans, monitoring of the effects was performed on food animals and food products and we have in detail documents a positive effect on all the bacterial species we have measured. Unfortunately no coordinated monitoring of the effects on human colonization in Denmark was implemented in connection with the different bans, mainly due to the need for ethical permission before samples from humans can be collected. Scientific studies from several other European countries, where the bans were implemented later than in Denmark, have however, documented a major positive effect in reducing the carriage rate of vancomycin resistant enterococci following the ban on avoparcin.

   In Denmark we can today with our monitoring in place document a low frequency of resistance to the antimicrobial agents which were banned. This picture is getting increasingly obscured by the fact that an increasing amount of food is imported from other countries, making it very difficult to point at specific sources in the future.

   Resistance in pathogens, common to both animals and humans, connected to human infections is so associated with antibiotic use in different reservoirs, that it is difficult to discern, which type or level of resistance derives from antibiotic use in humans and which in animals. Furthermore, it appears with increasing frequency, that at least in Denmark, most of the resistant bacteria humans acquire via food products derive from imported food (see DANMAP 2007 and 2008), which - since the data from antibiotic use in the veterinary sector is almost non-existent in most of the countries, that Denmark import food from – again makes it difficult to point at a specific antibiotic use reservoir.

   We can however see important decreases in resistance associated to the ban of growth promoters in at least two different bacterial pathogens: Campylobacter sp. and Enterococci. For Enterococcus faecium, we can prove a marked reduction in resistance to all growth promoters (See DANMAP, all reports up to 2008), and there have been very few vancomycin-resistant E. faecium infections in humans in the 2000´s. There are several reports in the literature on the decreasing carriage rate of Vancomycin resitant E. faecium in Europe after the growth promoter ban (e.g. Wolfgang Witte and coworkers).

   There has been a constant decrease in resistance associated to the ban of growth promoters in Campylobacter sp. Shown in the Figure 30 below from DANMAP 2008 one can follow the constant decrease in erythromycin resistance in Campylobacter coli, which started in 2000, the year where growth promoters were banned in Denmark. For C. jejuni the erythromycin resistance level has remained low in cattle, but resistance levels have been low in cattle in general due to the

relatively low antibiotic use in these animals (Fig. 29) (Dept. for Micorbiological Surveillance and Research, Statens Serum Institut)

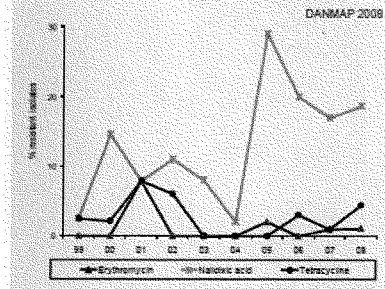


Figure 29. Trends in resistance to selected antimicrobials among Campylobacter jejuni isolates from cattle, Denmark.

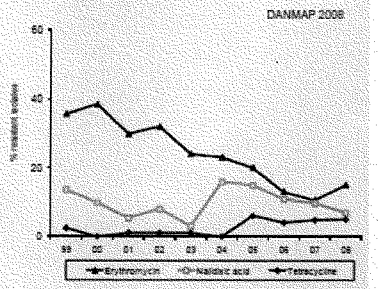


Figure 30. Trends in resistance to selected antimicrobials among Campylobacter coli isolates from pigs, Denmark

5. Yes, the number of farms has declined both in the swine industry as well as in the cattle industry. In the same time the average herd size has increased. This development has been seen for many years and is still going on as a consequence of a more and more modern and cost effective agricultural sector.

6. Antimicrobials used for animals are typically divided into two groups:
1) Critically important antimicrobials for human treatment (fluoroquinolones and 3. and 4 generation cephalosporins) and
2) Other antimicrobials, which can be used for treatment of animals with less risk of development of humanly critically resistant bacteria.

In 2002 fluoroquinolones were restricted in Denmark and can only be used if a current laboratory test shows that no other antibiotics can be used for that disease in that herd of production animals

Figure 1 describes the use of fluoroquinolones before the restrictions. Today the use of fluoroquinolones is still below 1-2 kg annually for all production animals.

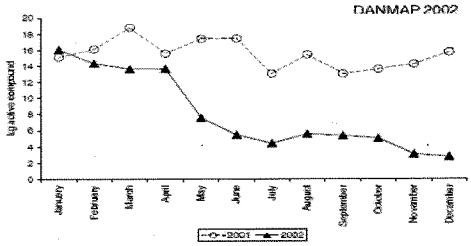


Figure 1. Total veterinary usage of fluoroquinolones in Denmark, 2001 and 2002

Using the consumption in 2001 as index 100, the development in usage of the critically important antimicrobials is described in figure 2.

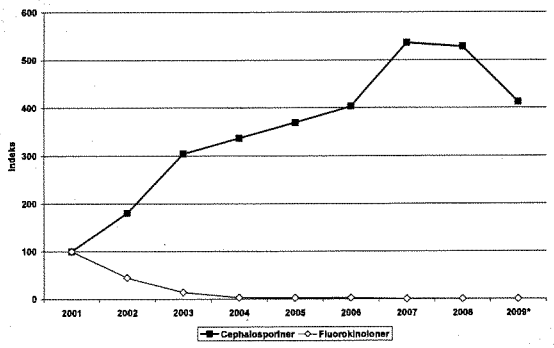


Figure 2 . Development in usage of critically important antimicrobials for swine from 2001-2009. (Source: DANMAP2001-2008, DTU, DVFA).
*The usage for december 2009 is estimated from figures from DTU for the january to november 2009 periode.

Only the figures for swine are shown, as the usage in other livestock productions is negligible.

HENRY A. WAXMAN, CALIFORNIA
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Congress of the United States
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COMMITTEE ON ENERGY AND COMMERCE
2125 RAYBURN HOUSE OFFICE BUILDING
WASHINGTON, DC 20515–6115

Majority (202) 225–2927
Minority (202) 225–3641

August 10, 2010

James R. Johnson, M.D., F.I.D.S.A., F.A.C.P.
Professor of Medicine, University of Minnesota
Fellow, Infectious Diseases Society of America
Infectious Diseases (111F)
Room 3B-105
VA Medical Center
1 Veterans Drive
Minneapolis, MN 55417

Dear Dr. Johnson:

Thank you for appearing before the Subcommittee on Health on July 14, 2010, at the hearing entitled "Antibiotic Resistance and the Use of Antibiotics in Animal Agriculture."

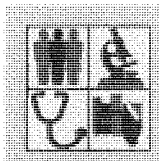
Pursuant to the Committee's Rules, attached are written questions for the record directed to you from certain Members of the Committee. In preparing your answers, please address your response to the Member who submitted the questions.

Please provide your responses by August 24, 2010, to Earley Green, Chief Clerk, via e-mail to Earley.Green@mail.house.gov. Please contact Earley Green or Jennifer Berenholz at (202) 225-2927 if you have any questions.

Sincerely,

Henry A. Waxman
Chairman

Attachment



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TEL:
FAX:
E-Mail Address:
Website:

IDSA
Infectious Diseases Society of America

August 23, 2010

The Honorable Henry Waxman
Chair, Energy and Commerce Committee
United States House of Representatives
Washington, DC 20515

via email to: Earley.green@mail.house.gov

Re: Questions Submitted for the Record

Dear Mr. Chairman:

In regard to the July 14, 2010, hearing on "Antibiotic Resistance and the Use of Antibiotics in Animal Agriculture," held before the Subcommittee on Health, one question for the record was submitted by Representative John Shimkus to James R. Johnson, MD, who testified on behalf of the Infectious Diseases Society of America:

> **Question**: *IDSA publishes a website called "Facts about Antibiotic Resistance," which identifies the specific bacterial infections that present the biggest challenges to doctors and healthcare facilities from resistance to antibiotics. Salmonella and campylobacter do not appear on that list. Of the seven bacteria listed on the website, do any have a connection to antibiotic use in food animals?*

Answer: IDSA is concerned about antibiotic resistance when it occurs in **any** type of disease-causing microorganism, especially if the resistance makes treatment of the associated infection more difficult, expensive, or toxic.

The specific resistant organisms mentioned on the "Facts about Antibiotic Resistance" page on the IDSA web site are of concern to IDSA because of the number and severity of associated infections, their recent and rapid emergence, the scarcity of treatment options, and other factors. These citations are neither comprehensive nor all-inclusive.

The list of all problem organisms and resistance phenotypes is much too extensive to be given full treatment on the web site. However, of various resistant organisms listed on the many pages of the IDSA web site, at least four have a connection to antibiotic use in food animals.

For example, *Salmonella* and *Campylobacter* are mentioned in 2004 and 2006, respectively, as organisms of concern with respect to acquired antibiotic

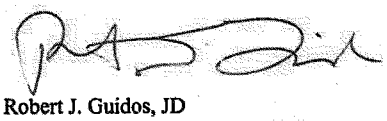
resistance (see pages 1 and 12 of the 2004 report, "Bad Bugs, No Drugs" (http://www.idsociety.org/BBNDWhitePaper04.htm) and page 2 of IDSA's 2006 "Statement on Use of 4th Generation Cephalosporins in Livestock" presented before the Food and Drug Administration's Center for Veterinary Medicine Advisory Committee (http://www.idsociety.org/WorkArea/DownloadAsset.aspx?id=16133)). For both of these bacteria, antibiotic use in food animals is a well-recognized contributor to their antimicrobial resistance, and food animals are established as the single most important source of these strains that cause human infections.

Multidrug-resistant *Escherichia coli* (*E. coli*) and methicillin-resistant *Staphylococcus aureus* (MRSA) (both of which are mentioned on the "Facts about Antibiotic Resistance" page, http://www.idsociety.org/Content.aspx?id=5650) also have connections to antibiotic use in animal agriculture. Multidrug-resistant *E. coli* strains are increasingly encountered in the community as well as the hospital. Several genetic-based studies suggest that most such strains are not human-source strains that acquired resistance while in humans, but instead likely were transmitted to humans from poultry which was already resistant. These studies also suggest that the poultry-source resistant *E. coli* likely became antibiotic-resistant while residing in poultry by conversion of poultry-source susceptible strains to resistant strains. This most plausibly would occur in relation to antimicrobial use in poultry.

MRSA strain ST398, which exhibits tetracycline resistance (unlike most other MRSA strains), is strongly associated with swine and swine production facilities, where tetracyclines typically are used extensively. Although as yet ST398 is a minor contributor to the global MRSA epidemic, this strain has caused serious and sometimes fatal infections in humans, mostly in persons with direct or indirect contact with swine or other food animals. This strain has recently been found in swine in Iowa and Illinois.

As you already know, antibiotic resistance is an important concern to IDSA, and we would be happy to provide any additional information as needed.

Sincerely,



Robert J. Guidos, JD
Vice President, Public Policy and Government Relations

HENRY A. WAXMAN, CALIFORNIA
CHAIRMAN

JOE BARTON, TEXAS
RANKING MEMBER

ONE HUNDRED ELEVENTH CONGRESS

Congress of the United States
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2125 RAYBURN HOUSE OFFICE BUILDING
WASHINGTON, DC 20515–6115

Majority (202) 225–2927
Minority (202) 225–3641

August 10, 2010

Christine Hoang, D.V.M., M.P.H., C.P.H.
Assistant Director
Scientific Activities Division
American Veterinary Medical Association
1931 North Meacham Road, Suite 100
Schaumburg, IL 60173

Dear Dr. Hoang:

Thank you for appearing before the Subcommittee on Health on July 14, 2010, at the hearing entitled "Antibiotic Resistance and the Use of Antibiotics in Animal Agriculture."

Pursuant to the Committee's Rules, attached are written questions for the record directed to you from certain Members of the Committee. In preparing your answers, please address your response to the Member who submitted the questions.

Please provide your responses by August 24, 2010, to Earley Green, Chief Clerk, via e-mail to Earley.Green@mail.house.gov. Please contact Earley Green or Jennifer Berenholz at (202) 225-2927 if you have any questions.

Sincerely,

Henry A. Waxman
Chairman

Attachment

AVMA American Veterinary Medical Association

1931 N. Meacham Rd.
Suite 100
Schaumburg, IL
60173-4360
phone 847.925.8070
800.248.2862
fax 847.925.1329
www.avma.org

August 18, 2010

Honorable John Shimkus
Committee on Energy and Commerce
2125 Rayburn House Office Building
Washington, DC 20515-6115

Dear Congressman Shimkus,

Thank you for the opportunity to address this issue on behalf of the veterinarians represented by the American Veterinary Medical Association (AVMA). Pursuant to the Committee's Rules, attached please find responses to your questions for the record referencing the July 14, 2010 Subcommittee on Health hearing entitled "Antibiotic Resistance and the Use of Antibiotics in Animal Agriculture.

1. **Does pain and suffering and premature animal death increase if you take away antibiotics that are preventing animals from getting sick?**

   The AVMA believes that without the use of antibiotics to prevent disease, there will be increased animal disease and therefore increased animal pain and suffering that would occur associated with the disease condition. Premature animal deaths can also occur if the disease becomes too advanced or severe for efficient treatment.

2. **Is it better to prevent livestock disease before there are serious outbreaks, or treat animals after they get sick? Would a veterinarian use larger doses of antibiotics to treat the disease than would be used in prevention?**

   The AVMA believes that it is more appropriate and judicious to prevent diseases before they occur rather than use greater doses and potentially stronger drugs to treat diseases after animals show clinical signs.

3. **Is there any specific evidence to show that there has actually been a decrease in antibiotic resistance infections in humans subsequent to the European ban on growth promoters?**

   No, there is no clear evidence of a significant decrease in antibiotic resistant infections in human as a result of the European ban on growth promoters. While resistance in *some* pathogens to *some* antimicrobials has declined, resistance in other pathogens has increased. More importantly, the same trends can be seen in other countries, such as the US, where no ban has taken place, therefore no causal relationship can be inferred.

4. **Would you describe for me what producers do today to implement judicious use guidelines and what these guidelines are?**

   Producer groups have their own judicious use guidelines that are a part of quality assurance programs such as PQA plus (the pork quality assurance program) or BQA (the beef quality assurance program). They are very similar to AVMA's Judicious Therapeutic Use of Antimicrobials species specific policies that can be found at http://www.avma.org/issues/antimicrobial_use_resistance.asp
   These principles outline objectives and strategies to optimize therapeutic efficacy and minimize resistance to antimicrobials to protect public and animal health. Specifically, the AVMA Judicious Therapeutic Use of Antimicrobials policy is attached in its entirety as Attachment A.

5. **I understand that the federal government is doing a great deal to collect data on possible antimicrobial resistance. One way we are doing that is through the National Antimicrobial Resistance Monitoring System (NARMS). The goal of the NARMS program is to collect data on, and facilitate the identification of, antimicrobial resistance in humans, animals and retail meats. What information has been gathered through the NARMS program?**

   NARMS gathers information on antimicrobial resistance patterns of specific bacteria from human enteric isolates, retail meats, and animal isolates. For example, in reviewing the information available through NARMS, the AVMA has found that human isolates of *Salmonella* spp. (non-Typhi) were more than twice as likely to be resistant in 1996 as compared to 2007 and *Salmonella* ser. Typhi (a human reservoir foodborne pathogen) are more than 4 times as likely to be resistant in 2007 as compared to 1999.

6. **It has been shown that a ban on growth promoting antibiotics in Denmark led to an increase in the use of therapeutic antibiotics, which are those that are considered medically-important in humans. Is it likely that restrictions on the use of growth promoting antibiotics in the United States will lead to the same trend?**

   The AVMA believes that bans on low level uses in the US, such as those that have taken place in Denmark, the Netherlands, and the EU, will result in similar effects – increased therapeutic uses (at higher doses and potentially more often in the same classes as important human drugs), and increased animal pain and suffering and potential death with associated diseases.

7. **I am concerned about the welfare of farm animals as every farmer in America is. In your professional opinion, is it wise to restrict the use of these products in feed to prevent diseases in animals? Is PAMTA in the best interests of animal wellbeing? Would banning many feed and water uses for prevention result in having to use more potent therapeutics as was the case in Denmark?**

No, restricting veterinary drug availability to prevent disease is not in the best interest of animal health and welfare. There is no question that if infectious diseases are not prevented *before* clinical signs are apparent, higher doses and potentially more important medications will need to be administered to treat the disease once it is widespread.

Respectfully,

Christine Hoang

Christine Hoang, DVM, MPH, CPH
Assistant Director, Division of Scientific Activities

c. Earley Green, Chief Clerk
Attachment

Attachment A

Judicious Therapeutic Use of Antimicrobials
(Oversight: FSAC; Approved by the AVMA Executive Board, November 1998; Revised April 2004, November 2008)

Position Statement
When the decision is reached to use antimicrobials for therapy, veterinarians should strive to optimize therapeutic efficacy and minimize resistance to antimicrobials to protect public and animal health.

Objectives
Support development of a scientific knowledge base that provides the basis for judicious therapeutic antimicrobial use.

Support educational efforts that promote judicious therapeutic antimicrobial use.

Preserve therapeutic efficacy of antimicrobials.

Ensure current and future availability of veterinary antimicrobials.

Strategies
Facilitate development and distribution of appropriate antimicrobial use guidelines by practitioner species-interest groups.

Improve scientifically based therapeutic practices through education.

Recognized Needs
Improved monitoring and feedback systems for antimicrobial use and resistance patterns.

Research to improve scientifically based therapeutic practices.

Judicious Use Principles
Preventive strategies, such as appropriate husbandry and hygiene, routine health monitoring, and immunization, should be emphasized.

Other therapeutic options should be considered prior to antimicrobial therapy.

Judicious use of antimicrobials, when under the direction of a veterinarian, should meet all requirements of a veterinarian-client-patient relationship.

Prescription, Veterinary Feed Directive, and extralabel use of antimicrobials must meet all the requirements of a veterinarian-client-patient relationship.

Extralabel antimicrobial therapy must be prescribed only in accordance with the Animal Medicinal Drug Use Clarification Act amendments to the Food, Drug, and Cosmetic Act and its regulations.

Veterinarians should work with those responsible for the care of animals to use antimicrobials judiciously regardless of the distribution system through which the antimicrobial was obtained.

Regimens for therapeutic antimicrobial use should be optimized using current pharmacological information and principles.

Antimicrobials considered important in treating refractory infections in human or veterinary medicine should be used in animals only after careful review and reasonable justification.

Consider using other antimicrobials for initial therapy.[1]

Use narrow spectrum antimicrobials whenever appropriate.

Utilize culture and susceptibility results to aid in the selection of antimicrobials when clinically relevant.

Therapeutic antimicrobial use should be confined to appropriate clinical indications.

Inappropriate uses such as for uncomplicated viral infections should be avoided.

Therapeutic exposure to antimicrobials should be minimized by treating only for as long as needed for the desired clinical response.

Limit therapeutic antimicrobial treatment to ill or at risk animals, treating the fewest animals indicated.

Minimize environmental contamination with antimicrobials whenever possible.

Accurate records of treatment and outcome should be used to evaluate therapeutic regimens.

[1]In this context, this principle takes into account development of resistance or cross-resistance to important antimicrobials.

Glossary:
*These terms are to be defined and utilized in the context of Judicious Therapeutic Use, with the intent of focusing on antimicrobials that may be of significance to human health. They are to be applied to the principles of Judicious Use outlined within the context of this document.

Antibiotic--a chemical substance produced by a microorganism which has the capacity, in dilute solutions, to inhibit the growth of or to kill other microorganisms.

Antimicrobial--an agent that kills microorganisms or suppresses their multiplication or growth.

Broad Spectrum Antimicrobial--a type of antimicrobial effective against a large number of bacterial genera; generally describes antimicrobials effective against both Gram-positive and Gram-negative bacteria.

Narrow Spectrum Antimicrobial--a type of antimicrobial effective against a limited number of bacterial genera; often applied to an antimicrobial active against specific families of bacteria.

Antimicrobial Resistance--a property of microorganisms that confers the ability to inactivate or elude antimicrobials or a mechanism that blocks the inhibitory or killing effects of antimicrobials.

Extralabel Use--extralabel use means actual use or intended use of a drug under veterinary direction, in an animal in a manner that is not in accordance with the approved labeling. This includes, but is not limited to, use in species not listed in the labeling, use for indications (disease or other conditions) not listed in the labeling, use at dosage levels, frequencies, or routes of administration other than those stated in the labeling, and deviation from the labeled withdrawal time based on these different uses.

Immunization--the process of rendering a subject immune or of becoming immune, either by conventional vaccination or exposure.

Monitoring--monitoring includes periodic health surveillance of the population or individual animal examination.

Therapeutic--treatment, control, and prevention of disease.

Veterinarian/Client/Patient Relationship (VCPR) -- A VCPR exists when all of the following conditions have been met:

1. The veterinarian has assumed the responsibility for making clinical judgments regarding the health of the animal(s) and the need for medical treatment, and the client has agreed to follow the veterinarian's instructions.

2. The veterinarian has sufficient knowledge of the animal(s) to initiate at least a general or preliminary diagnosis of the medical condition of the animal(s). This means that the veterinarian has recently seen and is personally acquainted with the keeping and care of the animal(s) by virtue of an examination of the animal(s) or by medically appropriate and timely visits to the premises where the animal(s) are kept.

3. The veterinarian is readily available for follow-up evaluation, or has arranged for emergency coverage, in the event of adverse reactions or failure of the treatment regimen.

Veterinary Feed Directive (VFD) Drug--The VFD category of medicated feeds was created by the Animal Drug Availability Act of 1996 to provide an alternative to prescription status for certain therapeutic animal pharmaceuticals for use in feed. Any animal feed bearing or containing a VFD drug shall be fed to animals only by or upon a lawful VFD issued by a licensed veterinarian in the course of the veterinarian's professional practice.

HENRY A. WAXMAN, CALIFORNIA
CHAIRMAN

JOE BARTON, TEXAS
RANKING MEMBER

ONE HUNDRED ELEVENTH CONGRESS

Congress of the United States
House of Representatives
COMMITTEE ON ENERGY AND COMMERCE
2125 RAYBURN HOUSE OFFICE BUILDING
WASHINGTON, DC 20515–6115

Majority (202) 225–2927
Minority (202) 225–3641

August 10, 2010

Richard Carnevale, D.V.M.
Vice President
Regulatory, Scientific and International Affairs
Animal Health Institute
1325 G Street NW, Suite 700
Washington, DC 20005

Dear Dr. Carnevale:

Thank you for appearing before the Subcommittee on Health on July 14, 2010, at the hearing entitled "Antibiotic Resistance and the Use of Antibiotics in Animal Agriculture."

Pursuant to the Committee's Rules, attached are written questions for the record directed to you from certain Members of the Committee. In preparing your answers, please address your response to the Member who submitted the questions.

Please provide your responses by August 24, 2010, to Earley Green, Chief Clerk, via e-mail to Earley.Green@mail.house.gov. Please contact Earley Green or Jennifer Berenholz at (202) 225-2927 if you have any questions.

Sincerely,

Henry A. Waxman
Chairman

1. How is antibiotic use by livestock producers tracked?

Since 1995 AHI has been surveying their members on antibiotic sales. The data is tabulated by pounds of various classes of antibiotics and antimicrobials such as tetracyclines and penicillins. AHI members manufacture about 85% of the antibiotics produced for the United States. The latest information on that survey is available at http://www.ahi.org/files/Media%20Center/Antibiotic%20Use%202007.pdf

Other surveys of antibiotic use that are periodically conducted are in the USDA National Animals Health Monitoring System where they query producers on the types and amounts of antibiotics used in particular species. These surveys are conducted every 3-5 years on an animal species basis.

Recently, the amended Animal Drug User Fee Act (ADUFA) of 2008 directed FDA to collect data on antibiotic use from animal drug sponsors beginning in calendar year 2010. The data was due to the agency in March 2010 and a report is expected from FDA later this year.

2. ***Is it true that the specific types of antibiotic resistance found in human medicine are not related to the use of antibiotics in animals, because the bacteria (causing these infections does not come from animals) or the drug of concern is not used in animals?***

Yes, the Centers for Disease Control and Prevention and the Infectious Disease Society of America, have identified the infectious bacterial diseases in humans that present the greatest concern for treatment with antibiotics because of resistance.

(http://www.cdc.gov/drugresistance/DiseasesConnectedAR.html)
(http://www.idsociety.org/Content.aspx?id=5650.)

- **Staphylococcus infections (MRSA)** – these are mainly hospital nosocomial infections but have been found in communities associated with schools and athletic facilities. These infections are a result of human to human transmission or contact with contaminated materials. IDSA says that 1% of people carry MRSA in their nasal passages. CDC investigates cases of MRSA and has concluded that animal contact is not a risk factor for these infections. Furthermore, they have also concluded that MRSA is not a foodborne infection and cannot be acquired by eating meat.

- **Acinetobacter baumanni** is an opportunistic pathogen associated with a high rate of infections in soldiers wounded in Iraq. It is most often associated with wound infections in hospitals and other medical facilities. It is inherently resistant to many antibiotics and has no connection to food animals or antibiotic use in food animals.

- **Vancomycin Resistant Enterococcus (VRE)** is another hospital nosocomial infection that has developed resistance due to extensive use of vancomycin in U.S. hospitals.

Vancomycin or drugs in its class have never been approved for or used in food producing animals in the United States.

- **Pseudomonas aeruginosa** is another opportunistic pathogen found in intensive care units that have become resistant to fluoroquinolone antibiotics. It occurs uncommonly in food producing animals where it can cause mastitis in dairy cows. Fluoroquinolones are not approved for use in dairy cows and furthermore Pseudomonas is not a foodborne pathogen.

- **Streptococcus pneumoniae is** resistant to several classes of antibiotics and is strictly a human pathogen that causes respiratory infections. This organism has no known connection to food producing or companion animals.

- **Neisseria gonorrhea** is strictly a human pathogen that causes venereal infections transmitted through human sexual contact. Resistance develops because of poor patient compliance with the prescribed course of antibiotic therapy. There is no connection with animals or antibiotic use in animals.

- **Drug resistant tuberculosis, Clostridium difficile, and Klebsiella species** are other bacteria that are mentioned in the IDSA fact sheet. There is no known connection between these pathogens and food producing animals.

Notably, bacterial diseases such as foodborne illness due to Salmonella or Campylobacter are not even mentioned but are the most likely infections that could be transmitted from food producing animals via uncooked meat or poultry. Apparently these infections are not considered a significant problem for treatment due to antibiotic resistance.

*3. **What is your reaction to the data that Dr. Khan of CDC presented allegedly linking animal antibiotic use and human health problems?***

Dr. Khan presented three charts that appeared to document a "temporal" relationship between the use of certain veterinary antibiotics and the finding of resistance in human isolates to support his contention that the science is "unequivocal" regarding the link between animal use of antibiotics and negative impacts on human health. In my opinion, representing this data as unequivocal is a clear example of jumping to conclusions without having all of the information available:

1. Slide entitled: "Fluoroquinolone approval in humans and poultry and percent resistance in human Campylobacter isolates, by year, 1989-90 and 1997-2008"

- This slide attempts to demonstrate that resistance to Ciprofloxacin increased the year after Baytril was approved yet the NARMS program only started the year following approval. No data had been collected on a national basis prior to that so it is not known what the percentage of resistance may have been prior to approval.

- The data in NARMS is based on Campylobacter isolates that CDC receives from state public health laboratories. The isolates represent bacterial cultures from both domestically acquired as well as those associated with foreign travel. CD has stated in FoodNet, an active surveillance program, that there is a three-fold risk factor for acquiring fluoroquinolone (FQ) resistant Campylobacter from foreign as opposed to domestic sources. Another publication out of the Minnesota reports that 70% or more of resistant Campylobacter infections had a history of foreign travel. Therefore, it cannot be conclusively stated that the evidence is unequivocal that the approval of FQ's in poultry in the U.S. is the primary cause of the resistance seen in human infections.

- Finally, even if some of the resistance was due to Baytril use in poultry, this still does not mean there will be greater human health harm. Campylobacter is usually a self limiting infection and not a candidate for antibiotic treatment. A review published in 2007 of nearly 11,000 cases of human Campylobacteriosis found that there was no difference in duration of disease between FQ susceptible and FQ resistant infections indicating that FQ treatment does not affect the course of the disease. The mere presence of some level of resistance in a bacterium does not automatically mean that there will be human harm or that infections cannot be treated.

2. Slide entitled: "Quinolone-resistant Salmonella Typhimurium DT104 (UK)"

- This slide marked with the World Health Organization logo represents data from isolates collected and analyzed by The UK Health Protection Agency's Laboratory of Enteric Pathogens. Dr. John Threlfall is the director of that laboratory and has published information on this Salmonella strain since the 1990's.

- First, the resistance that was reported was for quinolones, which is a precursor to the fluoroquinolone antibiotics. The specific drug that was tested was a compound called nalidixic acid which is not used to treat human infections. Nalidixic acid is not a fluoroquinolone, like ciprofloxacin, which are used in human medicine, have greater effectiveness than quinolones, and are less susceptible to developing resistance. There was no clinical resistance reported to ciprofloxacin in this study.

- Secondly, the chart stops at 1997. It is known that DT -104 is a multi-resistant Salmonella clone that was prevalent in the 1990's in the UK. Clones of several Salmonella serotypes have been known to increase and decrease in populations of

animals and people in the past irrespective of antibiotic use. A clone simply reproduces and passes its exact genetic makeup to the next bacterium and soon the population of bacteria is dominated by that particular serotype. If the data had been shown after 1997 it would have demonstrated an eventual decrease from 2000- 2004 from 50% to 28% of DT-104 and an overall decrease in resistance to antibiotics despite veterinary use.

- A paper published in 2006 **(E.J. Threlfall, et al, Assessment of factors contributing to changes in the incidence of antimicrobial drug resistance in *Salmonella enterica* serotypes Enteriditis and Typhimurium from humans in England and Wales in 2000, 2002 and 2004, International Journal of Antimicrobial Agents 28 (2006) 389-395)** concluded that :

"...In relation to published data on veterinary sales of antimicrobials in the UK, the findings demonstrate that changes in the incidence of resistance do not correlate with changes in veterinary usage. ...."For S. Typhimurium, the most important factor has been an overall decline in the occurrence of multiple drug-resistant S. Typhimurium definitive phage type 104."

It is unfortunate that the CDC presented clearly incomplete data on the relationship between antibiotic use in animals and human resistance. What may have appeared to be a direct relationship between the two was later shown not to be the case.

3. Untitled slide: Voluntary withdrawal of cephalosporins in Quebec.

- This is chart from the Canadian CIPARS program which is similar to the U.S. NARMS program which tracks antimicrobial resistance in foodborne pathogens in Canadian provinces. In 2005 Quebec recommended that poultry producers stop injecting chicken eggs with ceftiofur, a veterinary cephalosporin, approved in the U.S. It must be noted that injecting eggs with this drug is not an approved use in either Canada or the United States. The drug is approved only for injecting day old chicks and turkey poults to prevent early mortality. While the data shows a decrease in retail chicken and in human isolates, missing is information from chicken carcasses which is important to support the case that the antibiotic resistant Salmonella actually came from the farm.

- Furthermore, it is known that Salmonella Heidelberg as one of many strains of Salmonella was known to decrease in prevalence in chickens and humans over the same period of time in other Canadian provinces that did not prohibit use of the drug. So the decline in resistance in Quebec may have been due to the overall decline in prevalence of this Salmonella strain. The chart also shows that between 2000 and 2006 there was a greater than 50% reduction in cephalosporin use in humans which could also explain a decrease in resistance of human infections.

As a final note all three charts presented at the hearing were from studies with drugs approved only for therapeutic use. The subject of the subcommittee hearing focused on antibiotics used in feed for "non-therapeutic" purposes. No data was presented by any witness to link antibiotics used in feed to antibiotic resistance in human pathogens.

4. You said in response to a question that the evidence was not unequivocal that animal antibiotics are impacting human health, particularly for antibiotics used in feed. What is the evidence for your response?

- The mere finding of resistance in animals, people, or food products doesn't automatically equate to risk – Antibiotic resistance can be present with or without antibiotic use because a specific bacteria may be inherently resistant to particular antibiotics or the bacteria is a clone of another bacteria that has carried the resistance over through genetic transfer.

- The vast majority of antibiotic resistant infections in humans are in bacteria that do not come from animals – MRSA hospital and community infections, VRE, gonorrhea, strep pneumonia, tuberculosis, acinetobacter baummani, etc. (See question 1)

- Most of the antibiotics used in feed are not used to treat foodborne illness. The one exception, macrolides has very low resistance in Campylobacter of about 1-2%

- Quantitative risk assessments in all major classes of feed antibiotics have shown extremely low levels of human risk.

- Antibiotic resistance as seen in NARMS has been unchanged for 10 years for the feed additive antibiotics and historical data back to the 1970's shows the same general levels of resistance. Resistance developed early with the use of these drugs in humans and later animals and has essentially remained at those levels over decades of use.

- The World Health Organization concluded that antibiotic resistance problems in humans due to growth promoters were rare in Denmark before or after the ban (Impact of antimicrobial growth promoter termination in Denmark, Foulum, Denmark, 6-9 November 2002)

5. We commonly hear that "70 percent of all antibiotics are used for non-therapeutic purposes in animals." Do you know the source of that statement, and is it accurate?

- This "estimate" comes from a 2001 publication by the Union of Concerned Scientists called "Hogging It," in which they multiplied the number of animals times the amount of antibiotics they guessed were being used.
- The UCS estimates included 11,046,693 pounds of ionophores and other substances not used in human medicine, or 45 percent of their total estimated amount. Ionophores are compounds not used in human medicine and are excluded from the antibiotic resistance debate. In 2007, Margaret Mellon, one of the authors of "Hogging It," said, "In the more than 10 years I've been in this issue, they've never been considered antibiotics." Except when she counted them in "Hogging It."
- The UCS estimate included 43,000 pounds of efrotomycin use in swine. Efrotomycin has never been sold in the United States.
- The UCS estimate includes 1.4 million pounds of chlortetracycline and nearly 400,000 pounds of erythromycin are used in chickens. Poultry veterinarians, however, indicate that few, if any, of these products are used in chickens today.
- To get to "70 percent," UCS had to invent a definition for "non-therapeutic" that included disease prevention and control uses that FDA, OIE and Codex consider to be therapeutic uses.
- There are no publicly available estimates of human use of antibiotics. So, to come up with "70 percent," UCS came up with their own estimate.

6. Is there any specific evidence to show that there has actually been a decrease in antibiotic resistance infections in humans subsequent to the European ban on growth promoters?

- We know of no evidence that has conclusively linked a decrease in antibiotic resistant infections in humans to the ban on growth promoters in Europe. As stated previously, the main problems in human medicine are with bacterial infections that do not originate in food animals. Furthermore, the antibiotics used as growth promoters in Europe were the types that are generally not active against the bacteria that commonly cause foodborne illness that could come from animals. The report by a WHO expert panel, cited in my answer to question # 4 above confirmed this in their conclusion that " *...direct effects of the termination of growth promoters on resistance in Gram-negative bacteria(e.g. E.coli, Salmonella) were neither expected nor observed."*

7. Is there an increased food safety risk if growth promoting or preventative antibiotics are removed from livestock feed or water?

- There could be. Scientists and veterinarians believe that antibiotics even used for growth promotion in reality suppress subclinical infections caused by bacteria that can inhabit the intestinal tract of food animals. Therefore, the use of antibiotics in the early stages of production allow for a "healthy" gut and facilitate the more efficient utilization of nutrients allowing the animal to gain weight faster with less feed. One 2003 peer-reviewed article by Scott Russell at the University of Georgia demonstrated that there were higher Campylobacter counts on carcasses from flocks with airsacculitis infections as opposed to carcasses from flocks that were airsacculitis negative **(S. M. Russell, The Effect of Airsacculitis on Bird Weights, Uniformity, Fecal Contamination, Processing Errors, and Populations of *Campylobacter* spp.and *Escherichia coli,* 2003 Poultry Science 82:1326–1331)**. Airsacculitis is an intestinal tract infection of broiler chickens that can cause the intestinal tract to more easily rupture upon processing spreading bacteria to chicken carcasses.

- Another publication on a quantitative risk assessment on virginiamycin, a feed antibiotic in chickens, indicated that there could be increased human health risks from more pathogens reaching consumers if virginiamycin use is terminated (**Cox L.A. *Potential Human Health Impacts of Banning Antimicrobials Used in Food Animals: A Case Study of Virginiamycin.* Environ Int. 2005; 31(4):549-63.**

8. Are you aware of evidence demonstrating that reductions in antimicrobial use in animal agriculture could be associated with a negative impact on the health of humans?

- The two publications cited in my answer to question #7 indicates that reductions in antibiotic use that keep food animals healthy could lead to greater overall incidence of foodborne infections.

9. When FDA approves a new antimicrobial animal drug, does it take into account the drug's importance to human health?

a. What happens if FDA concludes that the drug is important to human health?
b. Does FDA not approve the drug for animals?
c. Does FDA put restrictions on its use?
d. Are there situations where Guidance 152 has resulted in more restrictive labeling of a product through the inherent risk mitigation steps that FDA can impose?

- FDA has always examined the impact of animal drugs including antibiotics for any on human health whether or not the drug is also important for treating diseases in humans. With antimicrobials, FDA requires the sponsor of a new antimicrobial product for food animals to demonstrate the drug is safe from any residues that may remain in the animal after use and that could also be present in meat, as well as evaluating the potential for an animal antimicrobial, that may also be medically important to humans, to select for resistance in certain foodborne pathogens that could be transferred to humans.

    - FDA will conduct a qualitative risk assessment on a new antimicrobial under Guidance for Industry # 152 and rank the drug as critically important, highly important, or important to human health based on criteria set forth in guidance. Depending on the ranking of the drug's importance it will affect the overall risk evaluation for the drug that is proposed for use in animal medicine and will affect whether or not the FDA approves the drug and if so, under what conditions of use.

    - The FDA could decide to not approve the drug for animals depending on the importance to human health ranking and the sponsor's proposed label claims and conditions of use.

    - FDA does require certain restrictions depending on the overall risk ranking of the antimicrobial. If the potential risk to human health is judged to be high then FDA can impose certain restrictions, such as, for use only in individual animals for short term therapy, and that it is only available on the order of a licensed veterinarian either as a prescription product or under a veterinary feed directive.

    - The experience with Guidance 152 has been that sponsors have tailored their applications for new antimicrobials to meet the inherent restrictions contemplated by the guidance. For example, it would be highly unlikely for any antibiotic ranked as critically important for human medicine to be approved by the FDA for extensive use in the feed of livestock or poultry.

10. Would you describe for me what producers do today to implement judicious use guidelines and what these guidelines are?

The AVMA, species-specific veterinary groups, and feed and producer groups have all worked with government agencies including FDA to produce Judicious Use guidelines for safe and judicious use of antimicrobials based on several principles for managing infectious diseases. The Judicious Use Principles are designed to minimize the need for antimicrobial use, but when needed, to use them properly, and to evaluate the outcome of the use.

These guidelines are used as the basis for producer education programs and represent an important effort on the part of the animal agriculture community to ensure that antimicrobials are used properly. Many producers have used these guidelines to create standard operating procedures for antimicrobial use on the farm. The National Pork Board has instituted the "**Take Care - Use Antimicrobials Responsibly Program.**" Take Care is based on five principles to guide antimicrobial use in pig production. It has been endorsed and adopted by numerous large and small producers. The National Cattlemen's Beef Association also operates under a Beef Quality Assurance program which stresses the use of FDA approved products only, that Judicious Use Guidelines be followed, and that any extralabel use be authorized by a veterinarian according to FDA regulations.

11. I understand that the federal government is collecting data on possible antimicrobial resistance. One way we are doing that is through the National Antimicrobial Resistance Monitoring System (NARMS). The goal of the NARMS program is to collect data on, and facilitate the identification of, antimicrobial resistance in humans, animals and retail meats. What information has been gathered through the NARMS program?

NARMS is a joint program between the FDA, USDA, and CDC which has been collecting and analyzing foodborne bacterial isolates from carcasses and human infections since 1996 and retail meats since 2002. The isolates are tested for antibiotic susceptibility to 17 different antimicrobial compounds. The program attempts to relate what may be coming through the food supply from animal sources that could affect human health. Over 50,000 Salmonella and Campylobacter samples have been tested in all three arms of the NARMS program. The data indicate that resistance rates in human infections to critically important antibiotics have been very low and have remained relatively steady over the years. Resistance rates in animals are generally higher than those seen in humans for several antibiotics indicating that bacterial resistant bacteria are not being always being directly transferred from animal derived food to humans. Resistance rates to older antibiotics, such as tetracycline and penicillin are higher than those for the critically important drugs, but have remained at those same levels for years based on data collected prior to the NARMS program. 81% of all human isolated Salmonella are susceptible to all antibiotics tested in the program.

12. It has been shown that a ban on growth promoting antibiotics in Denmark led to an increase in the use of therapeutic antibiotics, which are those that are considered medically-important in humans. Is it likely that restrictions on the use of growth promoting antibiotics in the United States will lead to the same trend?

Yes, there is every reason to believe that removing antibiotics from animal feed will cause an increase in disease and mortalities, particularly in young animals. Certainly, there has been a misunderstanding with the public and a negative perception of the value of low dose uses of antibiotics for growth promotion. These claims were established many years ago when antibiotics were first being used in animal production. There has not been a new growth promotion indication approved in more than 20 years for any antimicrobial considered medically important for human medicine. While the so called growth promotion indications imply that these uses simply "fatten" the animal, in fact, what many veterinarians and researchers believe is that their use functions in maintaining gut health by suppressing bacteria causing subclinical disease. Subclinical infections may not be readily apparent but can affect the animals' ability to efficiently utilize nutrients to reach its optimal production potential. This was most evident in Denmark when withdrawal of antibiotic growth promoters from pig production resulted in the outbreak of intestinal disease in weanling pigs leading to increased incidence of scouring with attendant increase in mortalities.

